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PRINCIPLES OF UTERINE GROWTH IN PREGNANCY*

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IT IS a generally accepted physiological fact that, when a function commences, the organ which performs it takes on an increased energy and activity which is proportional to the importance and duration of the duty which it has to perform. Although there is no exception to this general principle, it is nowhere more evident than in the organs of generation during pregnancy and, in particular, in the uterus, which, activated by the spark of fertilization, increases by weight over thirty times and by volume over two thousand times, all in somewhat under three hundred days.

There has been a considerable accumulation of uncoordinated anatomical, histological, and physiological data concerning uterine growth during pregnancy. However, evidence has been presented recently which proposes that this growth consists, at least in litter-bearing animals and in lower primates, of several separate phases, all following in orderly progression and all closely related one with the other. The physiological principles involved in each phase are, however, quite different.

According to the original concept,[1, 2, 3] the pattern of uterine growth in order to accommodate the products of conception falls into three distinct groups, a period of preparation, a period of proliferation, and a period of elongation.

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The period of preparation consists of a wave of myometrial hyperplasia which diminishes at nidation. The next period, proliferation, is one in which the uterus grows by hypertrophy and to a lesser extent hyperplasia. Finally, during elongation, the uterus increases in size by means of myometrial stretching, and not by actual growth.

The stimulus for active growth in the second period consists of both hormonal influence and intrauterine tension produced by the enlarging conceptus sites. The myometriogenic effect of the altered hormone patterns in pregnancy is a well recognized fact.[6-10] Moreover, the similar effect of distention of the uterine cavity is well known, even with an inert substance such as paraffin acting as the distensor.[4-7] Together these stimuli are responsible for the uterine growth in the first two periods of pregnancy.

During the second period, each conceptus site in the litter-bearing uterus is spherical in shape and the tension upon the uterine walls increases rapidly in accordance with physical principles reviewed elsewhere.[1, 3] The tension within the uterine tissues eventually acts detrimentally upon uterine circulation and myometrial ischemia ensues. This acute situation is abruptly relieved when the uterus undergoes a process of conversion in which each spherical conceptus site merges into a cylindrical uterus. Again, according to physical principles[3] there is an immediate reduction in tissue tension accompanied by restored myometrial circulation but diminished myometrial growth. Hereafter, uterine enlargement is accomplished by stretching of the myometrium with minimal or no new growth. The fetus matures rapidly during the final period in the cylindrical uterus.

It has been shown that uterine conversion occurs at a specific period of gestation in each specific litter-bearing species. Further, it will be noted that the term "conversion" has been applied to a phenomenon consisting of three parts: first, an abrupt decline in uterine growth, second, a change in the pattern of uterine enlargement, and third, an acceleration of fetal growth. Finally, the pattern of uterine enlargement in lower animals is seen to be related to conditions of uterine blood flow. In order to relieve the increasing myometrial ischemia during the second period of uterine growth, the separate spherical conceptus sites elongate into single cylindrical uterine horns. This mechanism, according to established physical laws, diminishes tension upon the tissues of the uterine wall and allows return of adequate maternal circulation. The maternal blood flow through the uterus remains adequate until close to term at which time the myometrium and its vasculature have reached their physiological limits of elongation and stretching. It has been demonstrated that at this point myometrial ischemia ensues once more and is not relieved until the onset of labor.

These principles have been observed, studied, and reported by others in litter-bearing animals[1, 2, 3] and certain primates *(Macacus rhesus)*.[11] This investigation is concerned with growth of the human uterus in pregnancy from a morphological, histological, and physiological viewpoint, together with the relationship of this growth to fetal accommodation and to complications of late pregnancy.

Material

The investigation consisted of two major parts as follows:

1. *A Radiological Study of Uterine Enlargement.*—

Fifteen normal white obstetrical patients were selected from the obstetrical clinic of the Johns Hopkins Hospital. No differentiation was made between primigravidas and multigravidas. Beginning at the eighteenth week of pregnancy each patient was subjected to lateral and anteroposterior soft tissue x-rays of the abdomen taken at regular intervals until term. The average number of exposures was ten, delivering, according to a radiological consultant, negligible radioation to the fetus. The cervix was identified by sterile Hegar dilators placed in the vagina with great care. Each patient studied delivered a normal viable child at term.

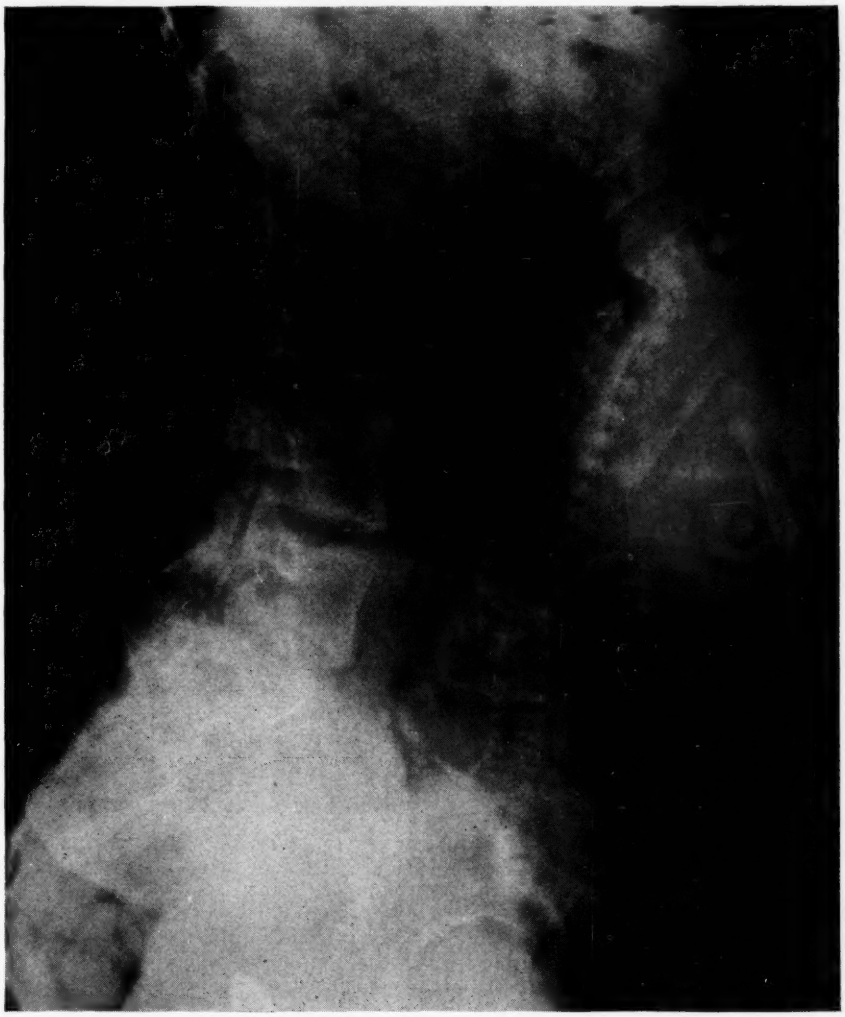

Fig. 1.—It is difficult to photograph soft tissue outlines of the uterus since a great deal of the information is elicited by transillumination. However, a representative photograph is shown. A Hegar dilator is placed against the cervix. The duration of gestation is thirty-three weeks and the uterus is easily visualized.

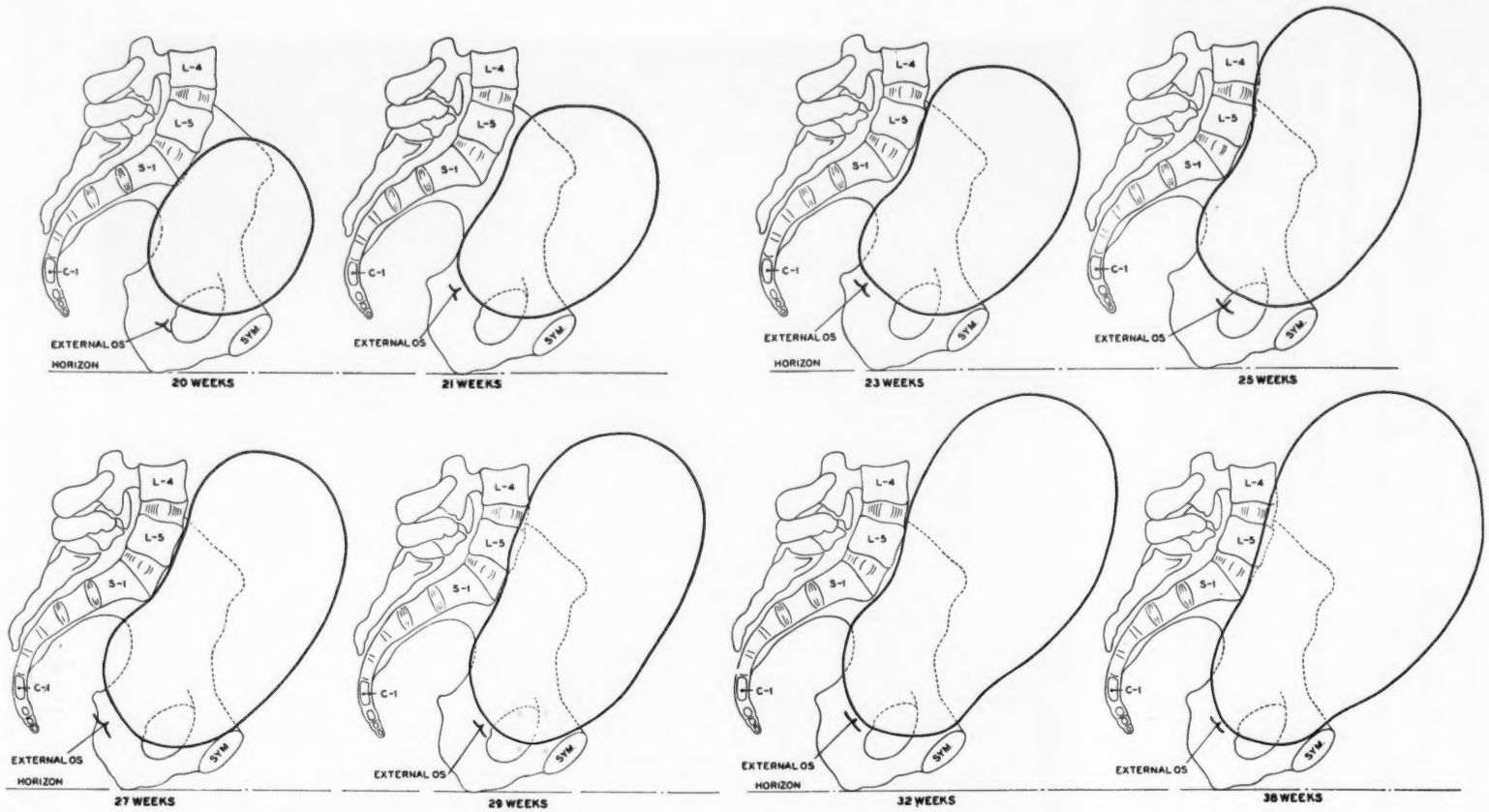

Fig. 2.—Shows diagrammatically (taken from actual x-rays) enlargement of the uterus following the twentieth week from the lateral view. Note rapid elongation to thirty-second week, then slight increase in anteroposterior diameter thereafter.

The purpose of this technique was to provide accurate outlines of the uterus under physiological conditions throughout pregnancy. In order to ascertain changes in shape by objective procedures, special methods were employed. The greatest uterine length (external os to crest of fundus) from the lateral view was plotted against the greatest fundal width (L/W). Fundal width refers to the greatest distance from the dorsal to ventral surface of the uterus. Obviously when L/W = 1, the uterus is spherical in shape and as L/W increases in value over 1 the lateral outline of the uterus becomes elliptical indicating that the uterus is becoming cylindrical in shape.

The only measurement recorded from the anteroposterior films was the greatest transverse diameter of the uterus as pregnancy progressed.

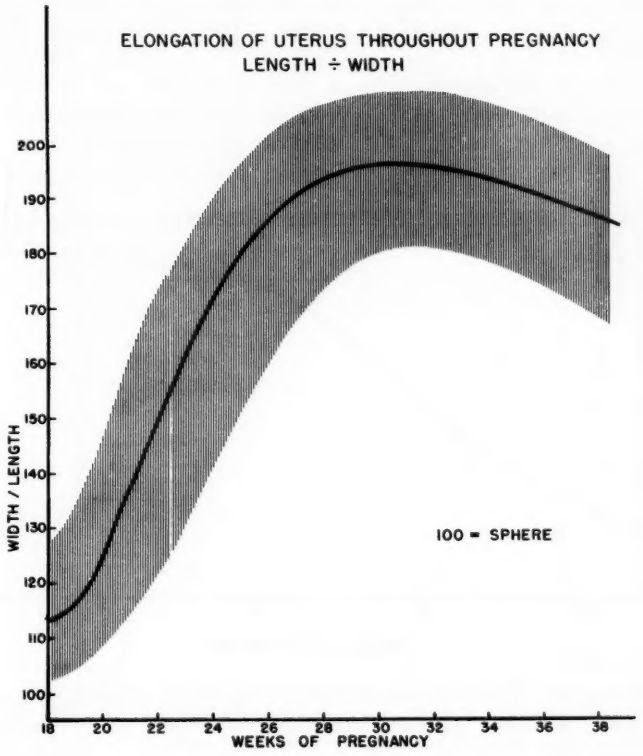

Fig. 3.—Graph showing elongation of human uterus. L = greatest length of uterus, W = greatest anteroposterior diameter. As L/W increase in value, the curve rises and the uterus is elongating. Note the rapid elongation until the end of the thirty-second week.

2. *Measurements of Uterine and Fetal Growth in Pregnancy.*—

The records of the Johns Hopkins Obstetrical Pathology Laboratory were searched for weights of uteri empty of contents removed at various stages of gestation for whatever reason. Obviously, those uteri with a pathological process which would affect their weight were not included in this study. Sixteen were found and their weights charted in Fig. 5. On the same chart were recorded measurements of myometrial thickness throughout pregnancy as obtained in the literature from a number of authors.[12-16] Finally, average fetal weights[15, 17] as pregnancy progressed were superimposed on the same graph.

Results

Figs. 2 and 3 demonstrate with extreme clarity the change in shape which occurs in uterine growth following the twentieth week. From the collected works of others[15, 16, 17] gathered in necropsy studies, it seems that the uterus at the onset of pregnancy is pear shaped and thereafter gradually assumes a spherical outline as the middle of pregnancy approaches. At any rate, our data show that, at the twentieth week, the uterus is definitely spherical in shape, judging from the lateral outline, and from this point forward it begins to elongate rapidly. Its outline therefore becomes cylindroid and remains so for the last twenty weeks of pregnancy. The rate of elongation diminishes somewhat at the thirty-second week. At this time there is some increase in the anteroposterior measurements (Fig. 3). However, as the diagram made from our x-rays demonstrates, the uterus is at all times cylindrical following the twentieth week. The diagrams in Fig. 2 represent average outlines obtained from characteristic x-rays. Fig. 3 consists of a graph plotted from measurements of length/width as described previously. This figure demonstrates again the rapid uterine elongation following the twentieth week and continuing till the thirty-second week.

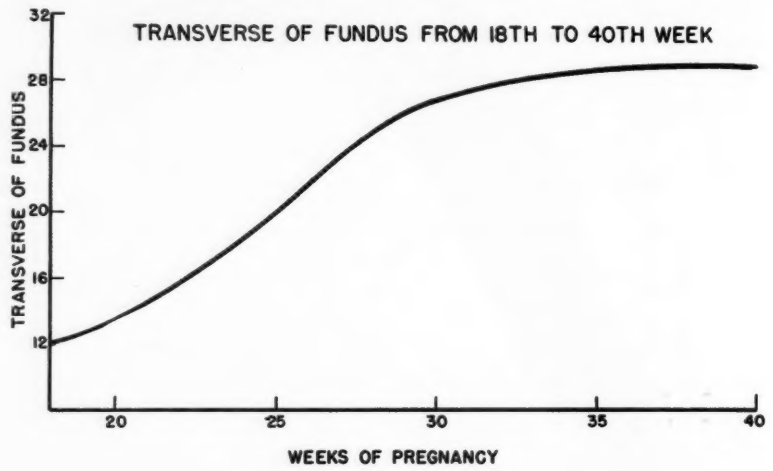

Fig. 4.—Transverse diameters of fundus taken at anteroposterior view. Values are plotted in centimeters and are greater than in life since there is x-ray distortion. However, all x-rays were taken at equal distance and therefore distortion is a constant factor. Note the increase in transverse diameter diminishes in last month.

Viewed from the front, a different impression of uterine enlargement is obtained (Fig. 4). During the elongation described above there is a steady increase in the maximum transverse measurement of the fundus which continues to term. This increase is most marked *prior* to the last month of pregnancy. During the last month, the rate of increase in transverse measurement decreases somewhat.

The composite graph (Fig. 5) shows a group of important correlations. Some of the data accumulated in this graph are of necessity sparse, and, standing alone, would be open to some question. However, taken in conjunction with data previously ascertained in other studies by other observers[1, 2, 3, 11] assurance is obtained as to the significance of our findings.

It will be seen that for the first twenty weeks of pregnancy, there is rapid increase of uterine weight. This is taken as presumptive evidence of actual growth. In support of this presumption, the myometrial thickness is seen to

be maintained for the first twenty weeks, although the uterus is becoming increasingly large.

Following mid-pregnancy, the uterus ceases to increase in weight and the myometrium becomes progressively thinner. This is taken as presumptive evidence of diminished uterine growth.

The last piece of evidence to be drawn from Fig. 5 is that, concomitantly with the uterine changes discussed above, there is rapid acceleration in the daily increment of fetal weight gain following the twentieth week. This is a fairly well recognized clinical fact and, although no physiological significance has previously been attached to this point, it is now apparent that there is nice apposition of these data with fetal growth as described in other animals. It has been suggested by work of others that the maturity of a fetus at birth in any species is not proportional to the total length of gestation but to the relative length of the postconverted phase.[18] Fetal maturity at birth is measured by the degree of fetal ossification, the presence of certain reflexes, and the tolerance of anoxia.

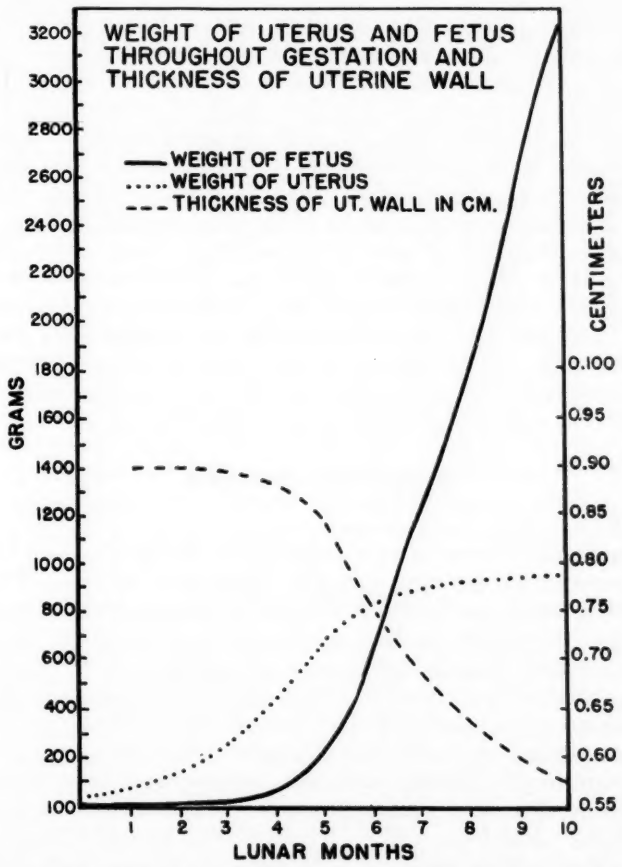

Fig. 5.—This expresses certain weights and measurements as a composite graph. Note that, in the vicinity of the twentieth week, uterine growth diminishes, the myometrium therefore begins to thin, and the fetus begins to increase rapidly in weight.

Comment

It is proper to suggest from the material presented thus far that uterine enlargement in pregnancy is a continuous process consisting of several separate phases in each of which the physiology is somewhat different. The uterus

in early pregnancy assumes a more or less spherical shape which it maintains for the first twenty weeks. According to certain measurements (myometrial weight and thinning) there is rapid growth of the uterus during this phase and slow growth of the fetus. Then, at the twentieth week, or shortly thereafter, the uterus begins to elongate rapidly and this is soon followed by an increase in the transverse fundal measurements. The rate of elongation is maximal until the thirty-second week and thereafter it diminishes. Transverse widening progresses through the remainder of pregnancy but at a slower rate following the thirty-sixth week.

Concerning real growth of the uterus, certain changes appear to supervene about the twentieth week coincident with and perhaps related to the actual alteration in outline pattern described. It will be noted in Fig. 5 that the greater part of utreine weight (empty of contents) is gained prior to the twentieth week. Moreover, although the myometrium is increasingly distended by the enlarging conceptus, it maintains the thickness of its walls (Fig. 5) up to the twentieth week. Both of these findings indicate that myometrial growth (hyperplasia and hypertrophy) must be taking place in early pregnancy. However, following mid-pregnancy, the curve of uterine growth levels off and measurements of the uterine wall show that it is becoming progressively thinner. This evidence indicates that hyperplasia and hypertrophy must be diminishing markedly in the last half of pregnancy. In this period the fetus is growing rapidly (Fig. 5), and to accommodate it the uterus must elongate and enlarge with equal rapidity. Since it has been demonstrated that actual growth is greatly curtailed in the last twenty weeks, it is evident that the mechanism of fetal accommodation must now consist largely of myometrial stretching. The composite graph demonstrates these concepts well. Such conditions necessarily place a limit upon the duration of gestation and they impose certain other conditions which may complicate gestation. Moreover, the pattern of primate uterine enlargement resembles that demonstrated in litter-bearing animals. It is therefore not improper to postulate the occurrence of vascular crisis at the critical period of conversion in human beings as has been shown to take place in the uterus duplex.

Supportive Evidence

1. *Histology.*—

There exists in the literature an abundance of histological evidence in support of the concepts of uterine growth discussed above. The ocurrene of hyperplasia during early pregnancy has been established beyond doubt.[7, 12, 30] At the same time hyperplasia has *not* been demonstrated beyond mid-pregnancy. There is considerable difference of opinion as to the source of new myometrium in pregnancy. Keiffer[19] felt the precursor cells to be fibroblasts whereas Joachimovits[22, 23] thought a special form of histiocyte was the parent cell. Stieve[12] concluded that not one, but several types of cells produced myometrium in pregnancy. These included myometrial histiocytes, wandering histocytes, lymphocytes, and fibrocytes. He is supported in this work by the evidence of Froböse[24] and Crandall.[25] Fischer-Wasels and Büngeler,[26] Luschka,[27] Moraller,[28] and Meyer,[29] as well as Salvatore,[21] believe that only pre-existing muscle cells give rise to new muscle cells during pregnancy. The evidence produced in most recent years by new histochemical and karyometric techniques[21] supports the last concept most strongly.

This sampling of the histological studies upon pregnant uteri reveals that there has been great diversity of opinion as to the source of new myometrium in pregnancy. On the other hand it reveals marked unanimity in the belief that hyperplasia does occur, and that it has ceased by mid-pregnancy (i.e.,

the twentieth week). It is altogether likely that hypertrophy continues for the total duration of pregnancy but, according to the measurements of myometrial weights and thicknesses, this hypertrophy is of a small degree.

A histological study by Ramsey[30] concerning the growth of myometrial and endometrial blood vessels during pregnancy in certain primates (*Macacus rhesus*) has recently been presented. During the study she describes the coiling of these vessels as pregnancy approaches the one hundredth day. Such coiling is apparently in excess of immediate demands, for following the one hundredth day these vessels begin to pay out and elongate until at term (one hundred sixty days) they are completely straight and widely dilated. Meanwhile it has been independently shown that conversion of the *Macacus rhesus* uterus occurs at the one hundredth day and at this point myometrial growth ceases.[11] Combining the data it was evident that the vasculature as well as the myometrium completes its growth prior to conversion, and, following the onset of uterine elongation, the myometrium begins to stretch and the blood vessels begin to uncoil. A similar detailed histological study of the vasculature of the pregnant human uterus does not yet exist. There is, however, some histological evidence that such coiling actually occurs in early pregnancy. Various authors[31, 32, 33] have described such a phenomenon during the first half of pregnancy. Moreover none have described such coiling at term. Consequently, although the data are meager, taken in conjunction with Ramsey's work, they point to a similar vascular phenomenon taking place in the human uterus during pregnancy. In other words, the myometrium and its vessels have completed their growth by mid-pregnancy. Thereafter, as the uterus elongates, the myometrium thins, and its vessels pay out.

2. *Morphology.*—

The actual pattern of uterine outlines which has been described in this paper has been recognized by other workers.[12] Standard textbooks[15, 16, 17] describe the uterus as becoming spherical prior to the fifth lunar month and then elongating into a cylinder until term. The background for this concept consisted of necropsy studies and clinical measurements. It is to be stressed, however, that no importance was attached to these anatomical changes of form. The study presented here confirms these patterns of enlargement under physiological conditions, but, more importantly, it shows the significant changes in uterine and fetal growth which accompany such morphological changes.

Clinical Correlations

The response of the uterus to physiological distention with the products of conception and to the altered systemic hormonal pattern is one of active hyperplasia and hypertrophy. This actual growth of the uterus includes the formation of new myometrium and probably coiling of the myometrial vessels. Such growth diminishes at the twentieth week of pregnancy and accommodation of the growing fetus thereafter is accomplished by myometrial stretching and vascular uncoiling. During this period the daily increment of fetal weight gain increases rapidly.

The cessation of growth at the twentieth week imposes certain conditions upon the uterus during the remainder of gestation:

1. The total duration of pregnancy must be limited since there is no new growth of myometrium and that which is present cannot indefinitely elongate. This has been observed in litter-bearing animals.

2. If, for any reason, there has been deficient myometrial growth prior to the twentieth week, it is reasonable to assume that the total duration of gestation will be less since myometrial stretch limits will be reached earlier.

This concept has been borne out experimentally. First, it has been demonstrated that a deficient diet will produce underdevelopment of the pregnant uterus.[34] Second, it is well known that an increased rate of premature delivery occurs in animals (including human beings) on a deficient diet.[34-38] The premature delivery occurs when the poorly developed uterus can no longer enlarge to accommodate the products of conception.

It is to be emphasized that this is not an attempt to explain away all premature deliveries as a function of diet. Nor is it an attempt to prove the onset of the labor occurs when myometrial stretch limits are reached. The study is intended to show that uterine growth is a factor, big or little, which has to be considered, and has not been considered, in the accommodation of a growing conceptus.

3. If there has been inadequate vascularization of the growing myometrium before conversion at mid-pregnancy, certain other conditions might arise. Such failure of vascular growth and coiling might be due to systemic diseases (diabetes, arteriosclerosis, etc.) or, again, to simple dietary deficiency. Whatever the cause, as the uterus elongates, its blood supply must eventually be in jeopardy. This will produce uterine ischemia, which in turn will produce placental ischemia. Thus we have disturbance in a basic growth mechanism associated with a variety of systemic disorders, which could produce *placental ischemia* late in pregnancy.

More and more investigators believe that placental ischemia is the basis of late pregnancy toxemias (eclampsia and pre-eclampsia). It has been as yet impossible to demonstrate a mechanism whereby placental ischemia could occur, and occur late in pregnancy. According to the mechanism of uterine growth just established it is in late pregnancy that the strain of inadequate uterine vascularization will be felt.

It bears repetition that it is not the author's intention to attempt the explanation of all complications of late pregnancy as disorders in uterine growth. However, functions of pregnancy as fundamental as uterine growth certainly must be normal to insure normal maintenance and termination of pregnancy, and it follows that, when abnormal uterine growth takes place, it must be accompanied by alterations from the expected course of events of a most severe nature.

Summary and Conclusions

1. Recent concepts of uterine growth during pregnancy in litter-bearing animals are reviewed. A relationship between morphology and growth of the uterus with certain vascular crises is presented.

2. The human uterus grows rapidly during the first twenty weeks of pregnancy. It is probable that this growth includes both the myometrium and its vessels, the latter growing in a coiled manner. The fetus begins to grow rapidly in the last half of pregnancy and uterine enlargement thereafter consists of elongation and myometrial stretching and vascular uncoiling because actual growth of uterine tissues has diminished.

3. It is safe to postulate that vascular crises may develop during growth of the human uterus since it follows closely the enlargement pattern of the uterus duplex in which such crises have been shown to occur.

4. The cessation of uterine growth at mid-pregnancy imposes certain conditions upon the last half of pregnancy:

a. the duration of pregnancy is conditioned by the myometrial stretch limits;

b. abnormally diminished myometrial growth during the first twenty weeks could produce premature labor;

c. abnormally diminished vascular growth during the first twenty weeks could produce premature uterine ischemia in the last trimester, a plausible basis of late pregnancy toxemia.

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SIMULTANEOUS RENAL CLEARANCES OF UREA AND URIC ACID IN THE DIFFERENTIAL DIAGNOSIS OF THE LATE TOXEMIAS

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IN THE absence of a reliable medical history, the differential diagnosis of the so-called late toxemias of pregnancy may be very difficult when the patient is seen in late pregnancy for the first time. If she has hypertension with some edema and but little proteinuria, she may have pre-eclampsia, hypertensive disease, or renal disease. Since the management and prognosis are somewhat different for each of these diseases, correct classification has more than academic interest. Also, patients with hypertensive disease, and probably those with renal disease, are especially susceptible to the superimposition of pre-eclampsia. The development of pre-eclampsia in these patients increases several fold the hazards to both mother and child (Chesley and Annitto[9]). This makes the early detection of pre-eclampsia especially important in such cases.

In the present paper, it will be shown that the simultaneous renal clearances of urea and uric acid usually make a clear-cut separation of the three diseases—both clearances are normal in uncomplicated hypertensive disease and both are low in renal disease, while in pre-eclampsia the uric acid clearance is disproportionately depressed.

As background, it might be well briefly to review the physiology of urinary excretion. In normal women, the rate of glomerular filtration averages about 116 ml. per minute, and in this glomerular filtrate the urea and uric acid concentrations are the same as in plasma. If all of the filtered urea and uric acid were finally excreted in the urine, the clearances of these substances each would be 116 ml. per minute.

In the case of urea, about 40 per cent of the amount filtered is reabsorbed by the renal tubules, when the urine volume exceeds about 2 ml. per minute. Thus, about 60 per cent of the filtered urea is excreted, and its clearance averages about 70 ml. per minute. This is called the maximal clearance, because with lower urine volumes more and more urea is reabsorbed as the urine volume diminishes. Therefore, below urine volumes of 2 ml. per minute the actual clearance of urea depends upon the urine volume, and there are as many "normal" clearances as there are possible urine volumes. Empirically, the actual clearance of urea when plotted against the urine volumes between 0.35 and 2 ml. per minute follows a power curve. From the assumption that this power curve is generally valid, one may calculate what the urea clearance would be at the standard urine volume of 1 ml. per minute, and thus obviate the necessity of remembering an almost infinite number of "normal" values. This "standard" urea clearance averages about 54 ml. per minute, which is taken as 100 per cent. For clinical purposes, the standard urea clearance is of great value in assessing renal impairment, but physiologically these clearances are not in good odor.

All of the urea reabsorbed, at any urine volume, is thought merely to diffuse passively back through the renal tubules, which are not completely impermeable to it. This is a salient point in our argument.

In contrast to urea, about 87 per cent of the filtered uric acid is reabsorbed. This tubular reabsorption of uric acid is not merely passive back-diffusion, the tubule cells *actively* reabsorb it. Evidence for this is seen in the facts that the uric acid clearance increases when the plasma level is increased,[5] the urine concentration may be less than the plasma concentration in diuresis,[5, 7] and the clearance is increased markedly when the tubular transfer mechanism is preempted by the simultaneous excretion of Diodrast[2, 16] or p-aminohippurate.[7]

When the urine volume falls below about 1 ml. per minute the uric acid clearance diminishes, following a power curve in which the square root of the urine volume appears.[6, 7]

The average normal plasma clearances (maximal) of urea and uric acid are about 70 and 15 ml. per minute, respectively, a ratio of roughly five to one. When the clearances are reported in terms of percentages of average normal, the ratio is, of course, one to one.

The groundwork for the present study was laid in the paper by Chesley and Williams,[10] in which it was reported that in pre-eclampsia the uric acid clearance is decreased to a greater extent than are the clearances of inulin and urea. The uric acid clearance in pre-eclampsia is low for two reasons:

1. The rate of glomerular filtration often is reduced somewhat, and
2. The tubular reabsorption of uric acid from the glomerular filtrate is increased.

The first factor, alone, would reduce the clearances of urea and uric acid proportionately. The second factor, which does not affect urea, is responsible for the disproportionate drop in the uric acid clearance. In pre-eclampsia, then, the renal tubules are overactive in reabsorbing uric acid from the glomerular filtrate, and the uric acid clearance falls.

The characteristic change in the blood chemistry, in pre-eclampsia, is a rise in the uric acid level without a proportionate rise in urea or nonprotein nitrogen. This is comprehensible in terms of what has been said above, the disproportionate drop in the clearance of uric acid leads to a disproportionate rise in its blood level.

The work of Chesley and Williams[10] was confirmed, in part, by Bonsnes and Stander,[3] who determined the simultaneous clearances of urea and uric acid in pre-eclampsia. They thought that a decrease in filtration rate (which they did not measure) could explain the lowered clearances and that only in exceptional cases need there be invoked an alteration in the rate of tubular reabsorption of uric acid. However, comparison of their simultaneous clearances of urea and uric acid, in the few data given, shows that the uric acid clearance was decreased more than was the urea clearance in every case but one, and they remark that in four cases the urea clearance remained normal while the uric acid clearance was low throughout the pre-eclamptic period.

Material and Methods

The determination of the simultaneous clearances of urea and uric acid has been part of our routine toxemia work-up for some time, and nearly every patient admitted for antepartum observation for toxemia has had these clearance determinations. Also, we have done the tests on a large number of outpatients from the clinic, both normal and possibly incipient toxemia patients. In all, 427 clearances have been done in 290 cases.

After draining the bladder early in the morning, two samples of urines were collected at intervals of about an hour. Blood was taken into an oxalated bottle

at sometime during the test. These collections have been made by nurses, and many clearances were not satisfactory because of poor checks as between the first and second hour's clearances (faulty urine collections). However, even with the faulty urine collections, the ratio of the urea to the uric acid clearance might be calculated.

Urea in blood and urine was determined by Van Slyke's manometric urease methods,[13] while uric acid was determined by a modification of the method described in the manual of the Rubicon Company.[14] In this modification, blanks were prepared by removing uric acid from portions of each urine specimen by treating with Lloyd's reagent. Plasma uric acid was determined in Folin-Wu filtrates; in precipitating the protein care was taken, as previously described,[10] to avoid precipitation of uric acid.

Maximal clearances (actual clearances) were calculated for urea when the urine volume was 2 ml. per minute, or more, and for uric acid when the urine volume exceeded 1 ml. per minute. Standard clearances were calculated when the urine volumes were below these limits but above 0.35 ml. per minute. All clearances were reported in terms of percentage of average normal.

Results

Normal Pregnancy.—Simultaneous clearances of urea and uric acid were determined in 84 normal pregnant women, ranging from the eighth to the fortieth weeks of gestation. The urea clearance averaged 119 per cent with a standard deviation of 30.9 per cent, and a range of from 45 to 175 per cent. The uric acid clearance averaged 112 per cent with a standard deviation of 30.0 per cent, and a range of from 45 to 215 per cent.

The uric acid clearance was less than 70 per cent in five cases (6 per cent), and more than 140 per cent in nineteen (22.6 per cent). The urea clearance was below 70 per cent in four cases (4.8 per cent), and above 140 per cent in twenty cases (23.9 per cent). The fact that nearly one-fourth of the patients had high clearances is interesting in the light of Bonsnes'[2] finding that the rate of glomerular filtration is often increased in pregnancy, dropping to the nonpregnant level only a few days before delivery. Excluding our patients who delivered within a week of the clearance determination, somewhat more than half had high clearances.

Five nonpregnant normal subjects showed average uric acid and urea clearances of 105 and 107 per cent, respectively.

The ratio of uric acid to urea clearance varied from 0.45 to 1.50 in the pregnant normal subjects, and averaged 0.94 with a standard deviation of 0.22. In other words, with a urea clearance of 100 per cent, the uric acid clearance might vary from 45 to 150 per cent. The ratio was less than 0.65 in eight, or 9.5 per cent.

Uncomplicated Hypertensive Disease.—The clearance findings in thirty-three hypertensive women without superimposed pre-eclampsia were indistinguishable from the findings in normal patients. The averages, ranges, standard deviations, and clearance ratios were almost identical with those for the normal subjects (Table I). Hypertensives with superimposed pre-eclampsia have been excluded from this group.

Renal Disease.—There are only three cases of definite renal disease in this series. In these women, both the uric acid and urea clearances were depressed equally (clearance ratios 0.86 to 1.08).

We have some interesting miscellaneous observations in nonpregnant patients with renal disease. In the early recovery stage of lower nephron nephrosis the actual clearances of uric acid and urea are essentially equal (in terms of percentage of normal clearances, this would give a ratio of about five to one in con-

trast to the normal one to one). As recovery progresses the uric acid clearance may fall while the urea clearance rises. This is another evidence for the active tubular reabsorption of uric acid, and is therefore germane to our argument.

When diuresis begins, in lower nephron nephrosis, the urine is very poorly concentrated, presumably because of back-diffusion of the crystalloids through the damaged tubules. Apparently urea and uric acid diffuse back almost equally, and the injured tubule is unable to reabsorb uric acid actively. With recovery, the tubules become progressively more impermeable, with the result that the urea clearance rises. At the same time, the active reabsorptive capacity improves, and the uric acid clearance falls.

In malignant hypertension, where there is severe tubular ischemia and hypoxia, the uric acid clearance is disproportionately high, presumably because of impairment of the tubular function. In terminal glomerulonephritis the same thing may happen; in one case, the urea clearance was 7 per cent while the uric acid clearance was 20 per cent of average normal. Brøchner-Mortensen[6] has also remarked that in renal disease the uric acid clearance is often maintained nearer normal than are the clearances of urea and creatinine.

TABLE I. SIMULTANEOUS CLEARANCES OF URIC ACID AND UREA, AND CLEARANCE RATIOS

	NON-PREGNANT NORMALS	PREGNANT					
		NORMALS	UNCOMPLICATED HYPERTENSION	RENAL DISEASE	UNCLASSIFIED TOXEMIA	PRE-ECLAMPSIA	HYPERTENSION, PRE-ECLAMPSIA
No. of cases	5	84	33	3	45	113	7
Uric Acid Clearance.—							
Mean	105	112	106	49	82	52	46
Standard deviation	-	30.0	33.7	-	27.2	18.8	15.6
Range, in percentage of mean	72-135	45-215	55-210	29-60	35-165	15-185	25-64
Urea Clearance.—							
Mean	107	119	118	52	122	95	97
Standard deviation	-	30.9	28.0	-	32.4	27.9	13.0
Range, in percentage of mean	89-142	45-175	65-185	27-71	55-185	45-185	72-118
Clearance Ratio, Uric Acid/Urea.—							
Mean	0.98	0.94	0.90	0.94	0.67	0.55	0.48
Standard deviation	-	0.22	0.27	-	0.16	0.17	-
Range	0.60-1.48	0.45-1.50	0.55-1.45	0.86-1.08	0.35-1.05	0.25-1.05	0.25-0.65

Pre-eclampsia.—In the 113 patients with definitely diagnosable pre-eclampsia, the uric acid clearance averaged 52 per cent, and was less than 70 per cent in ninety-seven cases (85.7 per cent). The range was from 15 to 185 per cent; the high clearance of 185 per cent was determined four weeks before the patient had diagnosable pre-eclampsia. The simultaneous urea clearances averaged 95 per cent, ranging from 45 to 185 per cent (Table I). The ratio of uric acid to urea clearance averaged 0.55, varying from 0.25 to 1.05, much lower than in the normal or hypertensive women. The clearance ratio was below 0.65 in ninety-three, or 82.2 per cent.

The degree of the decrease in the uric acid clearance bore no relation to the severity of the pre-eclampsia as judged by the systolic hypertension (Table II), diastolic hypertension (Table III), the maximal rate of weight gain in any week of the last trimester (Table IV), or the degree of proteinuria (Table V). If the patient has pre-eclampsia, the uric acid clearance usually drops, the average being about 50 per cent. So far as the clearance findings go, pre-eclampsia

TABLE II. THE URIC ACID CLEARANCE IN RELATION TO THE SEVERITY OF PRE-ECLAMPSIA, AS JUDGED BY THE SYSTOLIC BLOOD PRESSURE

MAXIMAL SYSTOLIC PRESSURE IN MM. HG	LESS THAN 140	140 TO 149	150 TO 159	160 TO 169	MORE THAN 170	ALL CASES
Uric acid clearance, mean	46.3	52.2	49.4	52.5	59.5	52.1
Range	35-65	25-115	15-105	15-85	45-95	15-115
No. of cases	8	35	32	20	18	113

is like pregnancy itself, the patient either has it or she has not. In many cases of barely diagnosable pre-eclampsia which has cleared up rapidly with treatment, the clearance has been as low as, or considerably lower than in severe pre-eclampsia. Moreover, when the whole clinical syndrome abates under treatment, the uric acid clearance remains low, or even drops further, and does not rise until after delivery. In one notable case of a patient who had some edema and an acute borderline hypertension for the first three days of hospitalization, the uric acid clearance dropped progressively from 46 to 17 per cent and the blood uric acid rose to 12 mg. per 100 ml. over a period of two weeks, although the pre-eclampsia was "cured" clinically.

TABLE III. THE URIC ACID CLEARANCE IN RELATION TO THE SEVERITY OF PRE-ECLAMPSIA, AS JUDGED BY THE DIASTOLIC BLOOD PRESSURE

MAXIMAL DIASTOLIC PRESSURE, MM. HG	LESS THAN 90	90 TO 99	100 TO 104	105 TO 109	110 TO 114	MORE THAN 115
Uric acid clearance, mean	75	49.5	53.6	51.7	50.7	53.5
Range	65-85	25-85	25-115	35-65	15-105	25-95
No. of cases	2	27	35	9	27	13

TABLE IV. THE URIC ACID CLEARANCE IN PRE-ECLAMPSIA, IN RELATION TO THE MAXIMAL RATE OF WEIGHT GAIN IN ANY WEEK OF THE LAST TRIMESTER

MAXIMAL WEEKLY WEIGHT GAIN, IN POUNDS	LESS THAN 1	1-2	2-3	3-4	MORE THAN 4	ALL CASES
Uric acid clearance, mean	51.0	52.3	52.1	54.3	53.0	52.8
Range	25-65	25-85	15-85	35-105	25-85	15-105
No. of cases	5	11	21	14	20	71

Fig. 1 shows a fairly typical case of pre-eclampsia, with the uric acid clearance remaining low, and dropping, until delivery. Post partum, there was a prompt return of the uric acid clearance to normal.

Unclassified Toxemia.—There were forty-five cases in which a definite diagnosis could not be made. Some were possibly borderline toxemias, while others were certainly toxemias but could not be classified for want of an adequate history. In this group the uric acid clearance ranged from 35 to 165 per cent, averaging 82 per cent. The clearance ratio averaged 0.67, and varied from 0.35 to 1.05. On the basis of the uric acid clearance, many of these cases probably were pre-eclampsia.

Of the forty-five, eighteen were previously normal patients suspected of having incipient pre-eclampsia. While all had edema, none had proteinuria or blood pressures of 140/90 for two days, and therefore they could not be classified as having pre-eclampsia. However, ten of these had uric acid clearances of less than 70 per cent, and eleven had clearance ratios below 0.65. Half of these patients, then, probably did have beginning pre-eclampsia, to judge from the clearance findings.

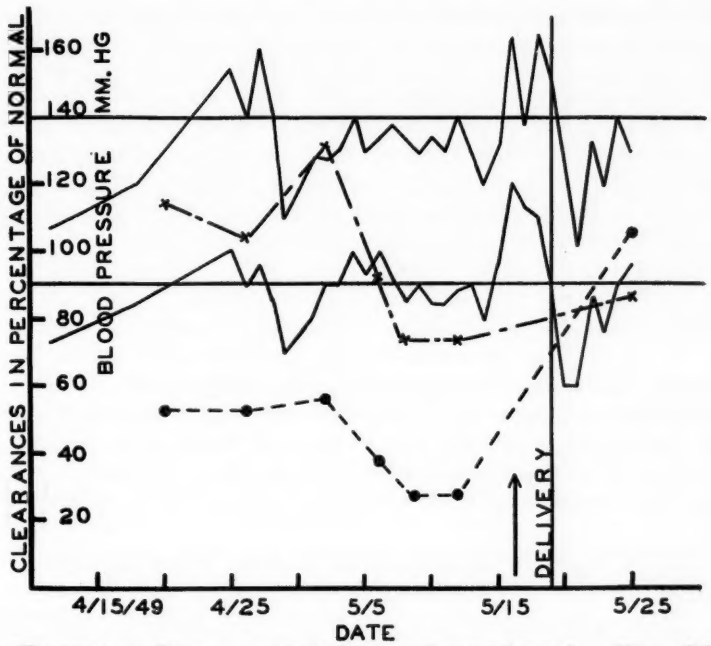

Fig. 1.—Clearance findings in a typical case of pre-eclampsia. The solid lines indicate the systolic and diastolic blood pressure reading, the broken line shows the urea clearance, and the dotted line the uric acid clearance. The arrow indicates the first appearance of proteinuria. The patient was in the hospital from the day on which hypertension was first noted. The first blood pressure shown is the average of the previously consistent readings in the clinic.

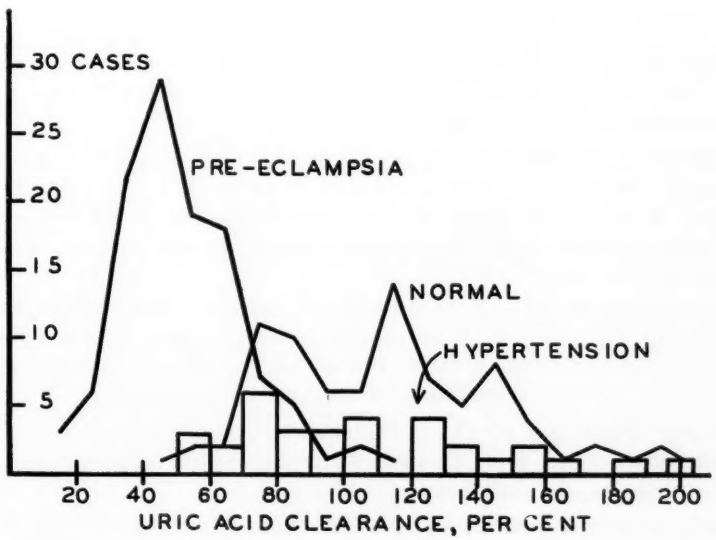

Fig. 2.—The distributions of the uric acid clearances in normal, pre-eclamptic, and hypertensive pregnancy.

TABLE V. THE RELATION OF THE URIC ACID CLEARANCE IN PRE-ECLAMPSIA TO THE AVERAGE SYSTOLIC BLOOD PRESSURE AND DEGREE OF PROTEINURIA

AVERAGE SYSTOLIC PRESSURE, MM. HG	LESS THAN 140		140 TO 159		160 TO 179		MORE THAN 180	
PROTEINURIA	LESS THAN ONE PLUS	MORE THAN ONE PLUS	LESS THAN ONE PLUS	MORE THAN ONE PLUS	LESS THAN ONE PLUS	MORE THAN ONE PLUS	LESS THAN ONE PLUS	MORE THAN ONE PLUS
Uric acid clearance, mean	65	38	53	48	58	54	45	55
Range	45-85	35-45	25-105	15-115	45-65	15-95	–	–
No. of cases	2	3	49	33	7	15	1	1

The Clearances in Differential Diagnosis.—Taking the 117 normal and hypertensive patients together, only ten (8.5 per cent) had uric acid clearances below 70 per cent. Of these ten, five had normal clearance ratios (above 0.65). Thus, 95.8 per cent of the normal and hypertensive patients had normal clearance findings (uric acid clearance above 70 per cent, or a clearance ratio above 0.65, or both).

In contrast, of the 113 pre-eclamptics, sixteen (14.2 per cent) had uric acid clearances above 70 per cent; of these sixteen, seven had abnormally low clearance ratios. Thus only nine of 113, or 8.0 per cent, had normal findings.

As between the normal and hypertensive patients on one side, and the pre-eclamptics on the other, there is an overlap of about 10 per cent. In nine cases out of ten, the clearance determinations will make a clear-cut separation of the pre-eclamptic from the uncomplicated hypertensive and normal patients (and those with renal disease). This is shown in Fig. 2.

Pre-eclampsia Superimposed Upon Hypertensive Disease.—In seven cases, normal uric acid clearances and clearance ratios were observed in patients with uncomplicated hypertension who later developed pre-eclampsia. In every case, the uric acid clearance dropped markedly during the pre-eclamptic phase, and returned to or toward normal a week or so after delivery. Two of these cases have been reported in detail in another publication.[8]

The uric acid clearance, in three of these cases, dropped *before* the appearance of edema, proteinuria, and increased hypertension. In one case the clearance dropped slowly only *after* the clinical diagnosis of superimposed toxemia was made, and in three cases the observations were not so spaced as to give any information on this point.

One hypertensive patient developed eclampsia. Two weeks before the convulsion, and ten days before diagnosable pre-eclampsia, the previously normal uric acid clearance had fallen from 101 to 64 per cent. Unfortunately, the patient delivered on the day scheduled for another clearance test.

Preclinical Diagnosis of Pre-eclampsia From the Clearance Findings.—As indicated above, the uric acid clearance, in hypertensive subjects, may drop before pre-eclampsia can be diagnosed clinically.

We have observations on only seven normotensive women who later developed pre-eclampsia. Four had normal uric acid clearances and clearance ratios at four and six weeks before pre-eclampsia could be diagnosed. One of these showed a significant drop in the uric acid clearance two weeks before pre-eclampsia was diagnosable. Three other patients, two with twin pregnancies and one with excessive weight gain, showed decreased uric acid clearances and clearance ratios two to four weeks before pre-eclampsia could be diagnosed.

As mentioned above under "unclassified toxemia," there were eighteen patients admitted for observation as having possible early pre-eclampsia. Two-thirds of these had either a lowered uric acid clearance or clearance ratio, or both.

Four patients with definite pre-eclampsia had normal uric acid clearances at the first determination, but later showed drops in their clearances. Two others, both with severe pre-eclampsia, had normal clearances in single determinations. Hence it would seem that the uric acid clearance need not drop before the clinical signs of pre-eclampsia become evident, although it may often do so.

Maximal Clearances.—About three-fourths of the urea clearances reported here were "standard" clearances. A separate analysis of the simultaneous maximal clearances is well worth while, for the purpose of evaluating the conclusions drawn from the data above. The urine volume exceeded 2 ml. per minute in twenty-nine of the normal pregnant patients, twenty-one of the hypertensive patients, and thirty of the pre-eclamptics. As Table VI shows, the clearance findings are quite in line with the data for the whole series.

In pre-eclampsia, the maximal urea clearances averaged 70 per cent of the mean for the normals, while the simultaneous uric acid clearances averaged 46 per cent. In other words, the urea clearance is depressed somewhat, presumably because of a decrease in the rate of glomerular filtration. The uric acid clearance is depressed to a greater degree, which strongly suggests that the tubular reabsorption is increased in pre-eclampsia.

In the hypertensives, both the urea and the uric acid clearances were normal, and again the simultaneous clearances separate the pre-eclamptics from the normals and simple hypertensives.

Pooling the data for the normals and the hypertensives, the coefficient of correlation (r) between the simultaneous clearances of urea and uric acid comes out as 0.71, a good correlation. For comparison, I have gone back over the records of the last seventy-five simultaneous clearance periods for inulin and urea, to determine the correlation between the urea clearance and the glomerular filtration rate. For these data, the coefficient of correlation is 0.79. The correlation between uric acid and urea clearances is almost as good as that between urea clearances and filtration rates.

TABLE VI. THE SIMULTANEOUS CLEARANCES OF URIC ACID AND UREA IN CASES WHERE THE URINE VOLUME EXCEEDED 2 ML. PER MINUTE (MAXIMAL CLEARANCES)

	NORMAL PREGNANCY	UNCOMPLICATED HYPERTENSION	PRE-ECLAMPSIA
Uric Acid Clearance.—			
Mean, in ml. per minute	16.7	15.0	7.80
Standard deviation	6.83	6.69	2.48
Range	8.4 to 39.0	6.2 to 33.9	2.9 to 13.7
Urea Clearance.—			
Mean, in ml. per minute	96.3	76.4	67.6
Standard deviation	37.7	41.0	16.5
Range	45 to 222	34 to 218	31 to 97
Clearance ratio,* uric acid/urea	0.87	0.98	0.58
No. of cases	29	21	30

*Clearance ratio calculated from percentages of normal, as in the other tables.

Comment

We believe that the data presented establish the value of the determination of the simultaneous clearances of uric acid and urea for the differential diagnosis of the late toxemias of pregnancy. In cases of hypertensive disease with superimposed pre-eclampsia, the tests will not identify the hypertensive component of the picture unless the clearances had been found to be normal earlier in pregnancy.

The renal disturbance leading to the drop in uric acid clearance may be closer to the fundamental pathologic physiology than are the signs of hypertension and proteinuria. This is suggested by the facts that the clearance sometimes falls before clinical pre-eclampsia becomes evident, that the clearance is as low in "minimal" pre-eclampsia as in severe, and that with clinical "cure" the clearance remains low, or may drop further. The last observation means that despite the disappearance of edema, hypertension, and proteinuria, there is a persistence of at least one characteristic abnormality of pre-eclampsia.

As pure speculation, it might be suggested that the renal tubule is also overactive in the reabsorption of sodium from the glomerular filtrate, and that this is the basis of the salt and water retention and edema.

Since there is no parallelism between the severity of the pre-eclampsia and the degree of depression in the uric acid clearance, it would seem to follow that the degree of hyperuricemia may not be a reliable guide to the severity of the toxemia. Stander and Cadden,[15] who wrote that the blood uric acid level in pre-eclampsia "gives us an accurate index of the severity of pre-eclampsia," based this concept largely upon the probably mistaken idea that the human liver destroys uric acid. We have by no means proved that the blood level increases solely because of the depression in the renal clearance, but the fall in clearance is sufficient to account for the rises seen. The work of Munnell[12] strongly suggests that the human liver does not destroy uric acid, and uricase has not been demonstrated in the human liver. There is some evidence that the liver may excrete uric acid in the bile.

The data presented have at least two aspects of theoretical interest. Although we frequently make a diagnosis of pre-eclampsia superimposed upon hypertensive disease, it is by no means certain that pre-eclampsia actually is present in the hypertensive who develops edema, proteinuria, and increased hypertension in late pregnancy. The fact that the uric acid clearance drops sharply in such patients is consistent with the view that they do have pre-eclampsia.

The other facet is the question as to the homogeneity of the cases classified as pre-eclampsia. Boyd,[4] on the basis of the ratio of the plasma phospholipids to total cholesterol, divided pre-eclamptics into two groups, the truly pre-eclamptic (22 per cent), and a group who were not literally pre-eclamptic (78 per cent). In the former group were patients with high ratios, such as were found in eclamptics. Dieckmann,[11] in unpublished work, has found that only a small proportion of pre-eclamptics react adversely to intravenous saline. This leads to the suggestion that the majority of pre-eclamptics are not pre-eclamptic. It would be interesting to know whether Boyd's and Dieckmann's separations would coincide. However, no division of cases can be made on the basis of the uric acid clearance. In the two eclamptics previously reported,[10] and in the one of the present series, the uric acid clearances were disproportionately low, the finding in the great majority of the pre-eclamptics.

We have assumed that the uric acid of the plasma is freely filterable, and that its concentration in the glomerular filtrate is essentially equal to that in the plasma. The disproportionately depressed clearance of uric acid in pre-eclampsia conceivably could depend upon decreased filterability rather than upon increased tubular reabsorption. Wolfson and Levine[17] have suggested that the major portion of the plasma uric acid circulates as a nonfilterable polymeric complex. If such a nonfilterable form of plasma uric acid were increased in pre-eclampsia, the effect would be a depression in the clearance. The depression in the uric acid clearance would be proportionately greater than any drop in the inulin or urea clearance. Our data can be interpreted on either basis.

Summary and Conclusions

Determinations of the simultaneous renal clearances of uric acid and urea were made in 290 pregnant women.

In eighty-four normal patients, urea clearance averaged 119 per cent of mean normal (70 ml. per minute), while the uric acid clearance averaged 112 per cent of mean normal (15 ml. per minute). The uric acid/urea clearance ratio averaged 0.94, and varied from 0.45 to 1.50.

In thirty-three patients with uncomplicated hypertensive disease, the means, standard deviations, ranges, and clearance ratios were almost identical with the findings in normal pregnant women.

In renal disease, the clearances are depressed in almost equal degree; in severe renal disease, the urea clearance may be decreased to a greater extent than is the uric acid clearance.

In 113 cases of pre-eclampsia, the urea clearance averaged 95 per cent, while the uric acid clearance averaged 52 per cent. The clearance ratio averaged 0.54, and ranged from 0.25 to 1.05.

In hypertensive disease with superimposed pre-eclampsia, the uric acid clearance drops disproportionately.

The simultaneous clearances make a good separation of pre-eclampsia, hypertensive disease, and renal disease. In pre-eclampsia, the uric acid clearance is disproportionately depressed, while both clearances are normal in uncomplicated hypertensive disease, and both low in renal disease.

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THE EXPERIMENTAL PRODUCTION OF IRREGULAR SHEDDING OF THE ENDOMETRIUM*

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FUNCTIONAL uterine bleeding has assumed a position of primary importance in the field of gynecology during the past fifteen years. Many noteworthy contributions concerning the nature of functional uterine bleeding, endometrial hyperplasia, and irregular shedding of the endometrium have appeared in the literature. The chief concern of this paper is to describe in detail the experimental procedures that have been conducted to reproduce the phenomenon of irregular shedding of the endometrium in a group of women well past the menopause. Women of this age were selected because of their availability and their potential usefulness in the bio-assay of the sex hormone.[1]

The literature on the subject of functional uterine bleeding has been more than adequately covered by Jones,[2] 1938, and McKelvey,[3] 1942. The first clinical description that can now be correlated with the established syndrome of irregular shedding of the endometrium was published in 1924 in the observations of Pankow,[4] who describes in detail three cases of menorrhagia in women whose previous menstrual periods had been quite normal. Curettage of the uterus produced an endometrium without an epithelial surface layer, with a compact stroma, and with collapsed glands. Pankow thought that these cases represented a delayed regeneration phase. In the German literature, Kaufmann and Hoeck,[5] 1926, and Robert Meyer,[6] 1930, continued the development of the theme of irregular shedding; but it remained for Traut and Kuder,[7] 1935, to present in English the first wel-devloped and integrated picture of the phenomenon. With the exception of the papers of McKelvey and Samuels,[8] and of Holmstrom and McLennan,[9] both in 1947, there has been no report in the literature of experimental attempts to reproduce this phenomenon of the endometrium or to demonstrate its etiology.

The fundamental work on the histology of the endometrium with its variations due to the rise and fall of hormonal influence was presented by Schroeder,[10] 1928. This effort has since been reviewed in detail by McKelvey,[3] 1942, and by Holmstrom and McLennan,[9] 1947. The fundamental histopathology of irregular shedding of the endometrium is the prolongation of the secretory type of glands and stroma beyond their average life expectance, within the functional layers of the endometrium. The following features also are constantly recognized in biopsies when irregular shedding is present: The surface epithelium is missing. The stroma is shrunken and basically composed of cells with large pyknotic nuclei and relatively little or no demonstrable cytoplasm. Stromal edema may be present to varying degrees. Many of the endometrial glands may be collapsed and/or star shaped, but most, even though collapsed, show evidence of secretory

*All of the medication used to conduct this experiment was generously supplied by the Schering Corporation.

activity. A relative increase in blood supply is noted and many arterioles near the surface of the functional layers of the endometrium are dilated and filled with blood, which characteristic may be the result of delay in involution of these arterioles. As the duration of vaginal flow continues, the number of secretory glands and the amount of secretory activity gradually diminish. However, glands showing the effect of progesterone may be seen in direct continuity with simple nonsecretory glands in a dense stroma characteristic of the estrogenic phase of the menstrual cycle. One should constantly bear in mind, when making a diagnosis of irregular shedding, McKelvey's admonition that "the outstanding feature of the endometrium of irregular shedding is its irregularity."

Novak,[11] 1940, has noted that while bleeding from the uterus at the time of normal menstruation generally lasts from four to seven days, the major portion of the endometrium has been shed by the end of the first seventy-two hours of menstrual flow. It is for this reason that the criterion has been established that a definitive diagnosis of irregular shedding of the endometrium cannot be made unless sufficient time has elapsed since the onset of vaginal bleeding.

Methods of Study

Postmenopausal women have been under a maintained estrogen influence (2 mg. of estradiol benzoate intramuscularly a week) for more than three years as part of a basic investigation into hormone replacement in the aged.[1] One group of patients, in addition to their maintained estrogen stimulation, have been under cyclic progesterone influence in an effort to simulate in so far as possible the sequence of events seen in the physiological menstrual cycle.[1]

The experimental group described above was placed on progesterone therapy and continued at a maintained dosage level from twenty-one to thirty days in an effort to determine whether the patients would escape the hormone influence and begin to bleed vaginally while on the medication. Whether those patients who demonstrated "break-through" bleeding would also note withdrawal bleeding subsequently when the experiment was discontinued was of interest. Table I lists the results obtained at both the 5 mg. and the 10 mg. progesterone levels.

TABLE I

PATIENTS* IN EXPERIMENT	DAILY PROGESTERONE DOSAGE†	PATIENTS SHOWING "BREAK-THROUGH" BLEEDING	ONSET OF "BREAK-THROUGH" BLEEDING	PATIENTS SHOWING WITHDRAWAL BLEEDING
8	5 mg.—21 days	4	17th-20th day	8
7	10 mg.—30 days	5	19th-30th day	7
7	10 mg.—36 days	7	17th-36th day	7

*All patients on 2 mg. estradiol benzoate a week.
†All medication given intramuscularly.

As noted in Table I, when patients (with satisfactory estrogen levels) are placed on 5 mg. of progesterone intramuscularly a day, the average patient will "break-through" and will start vaginal spotting somewhere between the seventeenth and twentieth day of the maintained progesterone influence. If, however, in a similar situation, the well-stimulated uterus is subjected to the influence of 10 mg. of progesterone a day, the average "break-through" time will be between twenty and thirty days. The "break-through" time of such levels as 25, 50, or 100 mg. of progesterone a day have not as yet been determined. Under present consideration, however, are attempts to suppress "break-through" bleeding once it occurs by doubling, tripling, or quadrupling the progesterone dosage at the time that spotting is first noticed.

Of major import in the etiology of irregular shedding is the histopathology that has been observed in routine biopsies taken in those patients who were maintained on progesterone until "break-through" bleeding occurred. Biopsies were taken frequently during the course of progesterone administration, and attention was first called to the possible reproduction of the phenomenon of irregular shedding by biopsies taken three days after the onset of vaginal bleeding.

These biopsies at first suggested that one aspect of irregular shedding might be demonstrated coincident with the work on the "break-through" bleeding experiments. The sections are merely suggestive. Biopsies were taken as noted on only the third day after the onset of bleeding, and could never be used to establish a conclusive diagnosis for this reason.

Figs. 1 through 3 represent an endometrial biopsy that was obtained three days after the onset of progesterone "break-through" bleeding (eighteenth day of 5 mg. per day) in a 76-year-old individual. Fig. 1 shows the still-retained surface epithelium, the collapsed, star-shaped glands with nuclei in basilar position, minor secretory activity in a few of the glandular cells, and a modest density of the stroma in which the stromal cells are intermingled with numerous red blood cells. Fig. 2, a second field in the same biopsy shows, however, more secretory activity of the endometrial glands. The intracellular edema and pale nuclei of the secretory cells are very much in evidence. The low-grade relatively exhausted secretory activity is clearly in evidence. Of particular interest in Fig. 3 are the intercellular fluid, red blood cells, secretory activity of the two glands of the lower part of the field, and the reverting characteristics of the gland in the superior portion of the field. This biopsy offers the suggestion that the endometrium was being irregularly stimulated or at least was reacting irregularly to a low level of progesterone.

Since the early specimens described above were very suggestive of irregular shedding of the endometrium, a portion of the experiment was repeated for the primary purpose of obtaining later biopsies. The seven patients were placed on a daily dosage of 10 mg. of progesterone to be continued until "break-through" bleeding occurred, and as long thereafter as was necessary to obtain the desired biopsies. Five members of the group broke through to bleed between the seventeenth and the twenty-eighth days of therapy. The other two patients broke through on the thirtieth and the thirty-sixth days. Two different areas of a single biopsy taken 10 days after the onset of "break-through" bleeding (twenty-eighth day) are shown in Figs. 4 and 5. The tissue in Fig. 4 shows small tubular glands with centrally placed nuclei in a moderately compact stroma (proliferative type) while the adjacent field in Fig. 5 contains glands of the early secretory type. An exhausted, flattened, atrophic type of surface epithelium is present. It is obvious that although these biopsies suggest irregular shedding, they do not meet all of the criteria previously outlined in this article. This point will be more fully dealt with in the discussion.

TABLE II

PATIENTS* IN EXPERIMENT	DAILY PROGESTERONE DOSAGE†	PATIENTS SHOWING "BREAK-THROUGH" BLEEDING	ONSET OF "BREAK-THROUGH" BLEEDING	PATIENTS SHOWING WITHDRAWAL BLEEDING
8	25 mg.—7 days 10 mg.—7 days 5 mg. until bleeding occurred	8	18th-24th day (4th-10th day of 5 mg. phase)	8
9	Same as above	8	21st-31st day (7th-17th day of 5 mg. phase)	9

*All patients on 2 mg. estradiol benzoate a week.
†All medication given intramuscularly.

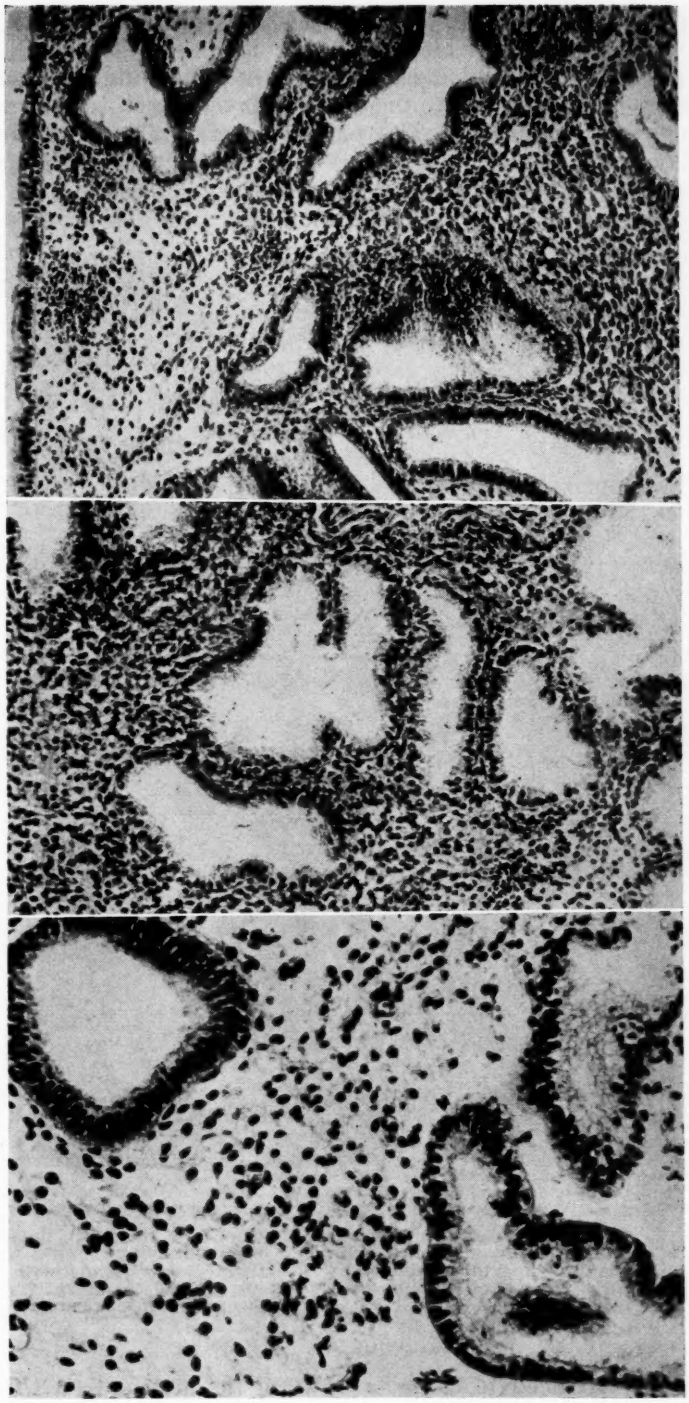

Fig. 1.

Fig. 2.

Fig. 3.

Figs. 1, 2, and 3.—Various areas of a single endometrial biopsy obtained three days after the onset of "break-through" bleeding from a patient receiving 5 mg. of progesterone daily. Fig. 1 shows the still-retained surface epithelium, collapsed glands with nuclei in a basilar position, minor secretory activity in a few of the glandular cells, and a modest density of the stroma. Fig. 2 shows more pronounced secretory activity of the glands with considerable intercellular edema. In Fig. 3 may be noted two secretory glands in the lower part of the field and the reverting characteristics of the gland in the superior portion of the field.

As an alternate approach to the problem, and with the basic knowledge provided by the "break-through" bleeding experiments, it was decided to emulate, in so far as possible, the sudden rise of progesterone influence common to the normal ovulatory peak and then to provide a delayed involutionary phase of prolonged progesterone exhibition. The patients were started on 25 mg. of progesterone a day, kept at this level for seven days; reduced to 10 mg. a day for

Fig. 4.

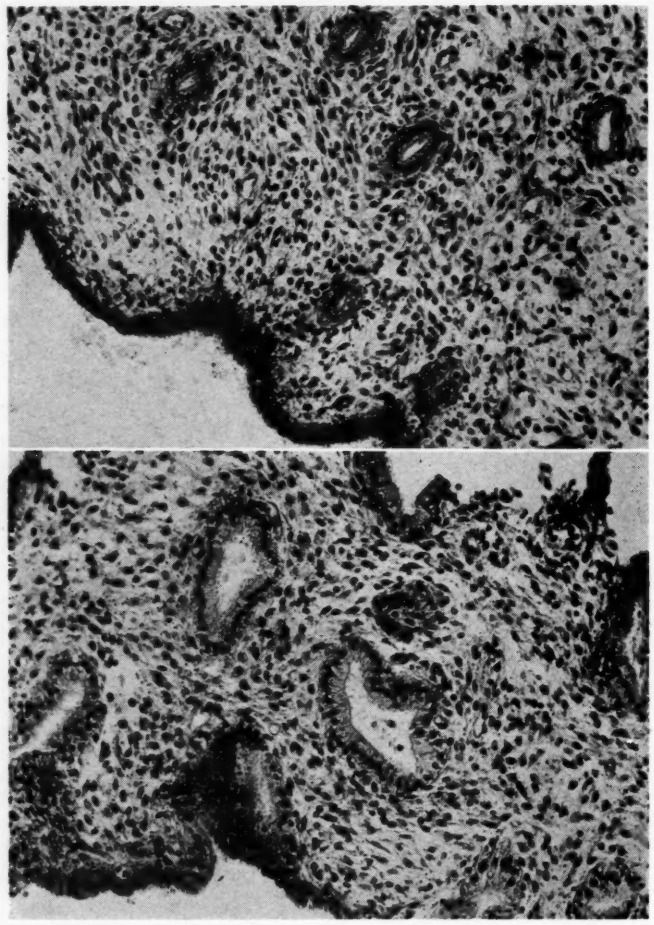

Fig. 5.

Figs. 4 and 5.—Two fields from a single biopsy obtained on the tenth day after the onset of "break-through" bleeding from a patient who had been receiving 10 mg. of progesterone daily for thirty-eight days. In evidence in Fig. 4 are the tubular glands with nuclei in mid-postion embedded in fairly compact stroma characteristic of the proliferative phase. Fig. 5 shows glands in early secretory phase. Note the presence of intact surface epithelium in both of these figures.

seven days, finally reduced to 5 mg. a day and maintained on this level until bleeding occurred (Table II). The experiment was conducted twice to check the basic information of "break-through" time in relation to the gradual reduction of progesterone influence. Biopsies were taken on these patients at the 25, 10, and 5 mg. levels before bleeding occurred, and boipsies were also obtained subsequent to the onset of vaginal spotting. The onset of withdrawal bleeding following the final withdrawal of progesterone influence was also noted.

It is evident that in the double run of the above-described experiment bleeding occurred anywhere from the fourth to the seventeenth day of the 5 mg. stage. It is interesting to note that one patient, although bleeding on the ninth day at 5 mg. level in the first experiment, failed to "break-through" on the second experiment even when the therapy was continued for a length of thirty days. In all instances, after the 5 mg. dosage level of progesterone was discontinued, the patients had exacerbations of vaginal bleeding demonstrating withdrawal bleeding in addition to their previously established "break-through" bleeding.

Figs. 6, 7, and 8 illustrate the results of the experiments described above. These photomicrographs represent biopsies taken on the second and the fifth days after the onset of "break-through" bleeding in patients who were being maintained on the regimen of decreasing progesterone levels detailed above. Each biopsy demonstrates some of the characteristics of irregular shedding of the endometrium. Fig. 6 shows gross irregularity of both glands and stroma although the biopsy was taken only two days after the onset of "break-through" bleeding. Figs. 7 and 8, a biopsy taken on the fifth day after the onset of "break-through" bleeding, show an area of typical proliferative endometrium adjacent to an area in which the glands exhibit rather marked secretory activity.

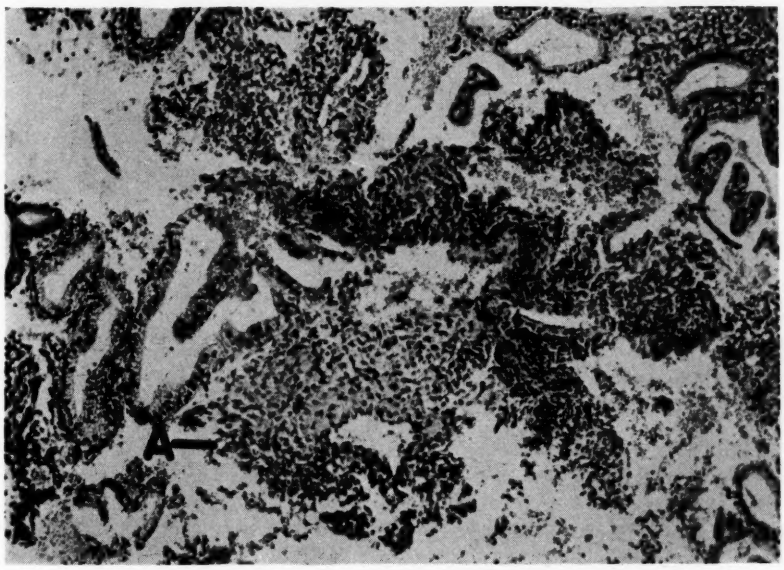

Fig. 6.—Biopsy taken on the sixteenth day at the 5 mg. level in the decreasing-dosage progesterone regimen, two days after the onset of "break-through" bleeding. Note the extreme irregularity of glands and stroma. Groups of both secretory and proliferative type glands may be seen in different areas of this single field. *A* indicates a large group of deciduoid cells.

In evidence in Fig. 8 are the star-shaped glands and shrunken stroma often mentioned in connection with irregular shedding of the endometrium. Fig. 9 demonstrates a further characteristic of this phenomenon, the fading and, in one area, the total absence of surface epithelium.

Comment

It has been suggested that irregular shedding of the endometrium is produced by prolongation of the corpus-luteum influence past that time at which the patient generally starts vaginal bleeding. That this is true has been proved rather conclusively by the excellent work of McKelvey and Samuels,[8] 1947, in demon-

strating pregnanediol glucuronidate in the urine of menstruating women in whom endometrial biopsies noted the cytological characteristics of irregular shedding. A primary possibility is that the corpus luteum of menstruation involutes slowly, thus reaching that level at which "break-through" bleeding occurs by slow reduction in the amount of progesterone that is being produced. The opposed possibility is that the corpus luteum of menstruation never achieves completely satisfactory development, and, as a result, produces a low level of progesterone throughout the luteal phase of the cycle, again allowing "break-through" bleeding to occur.

Fig. 7.

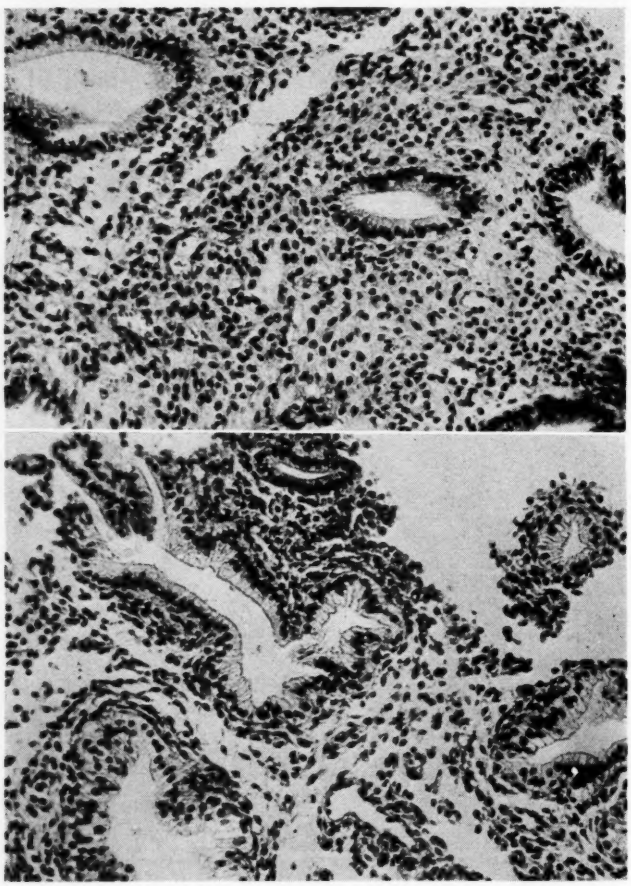

Fig. 8.

Figs. 7 and 8.—Two fields from the same biopsy taken on the fifth day after the onset of "break-through" bleeding. Fig. 7 shows primarily proliferative type glands in a mixed stroma. Fig. 8 demonstrates star-shaped secretory glands in a stroma which evidences some shrinkage around the glands.

The essence of the two experiments described above is the clear demonstration of the production of irregular shedding of the endometrium by the simulation of slow involution of the corpus luteum of menstruation described in detail in Table II, and the highly questionable production of irregular shedding by the low-level progesterone experiments described in Table I. It is evident that progesterone "break-through" bleeding must occur to produce the picture of irregular shedding of the endometrium. It is also obvious that irregular shedding may not be always reproduced by the variations of progesterone dosage that will stimulate "break-through" bleeding.

Of major clinical importance is the evidence that long-maintained progesterone influence, whatever the source, may cause "break-through" bleeding. Ultimately the development in the endometrium of the cytological picture of irregular shedding may occur. In order to establish a diagnosis it is of primary importance to procure the necessary endometrial biopsies at least five days after the onset of bleeding. The clinical diagnosis is missed in many instances by this one failure in timing. The reported incidence of irregular shedding varies from one-third to one-twelfth of those cases listed as functional uterine bleeding. A tremendous amount of attention in the literature has been paid to excessive or unopposed estrogen with an easily definable resultant hyperplasia of the endometrium as a cause of functional uterine bleeding. Insufficient time and effort have been devoted to its direct counterpart, that of prolonged or relatively unopposed progesterone influence as an additional cause of functional uterine bleeding.

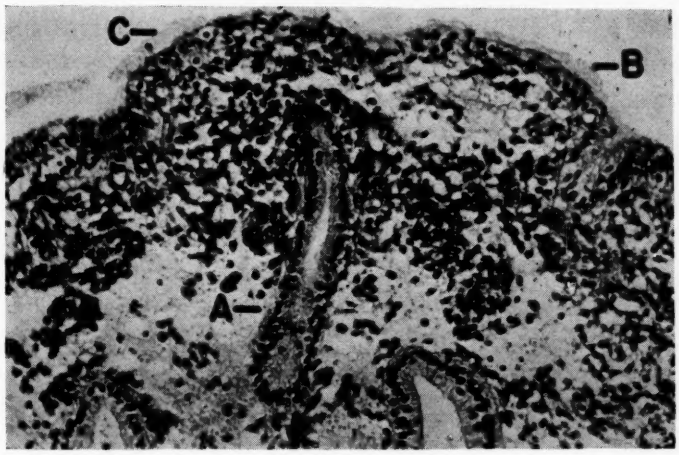

Fig. 9.—Biopsy taken on the sixth day after the onset of "break-through" bleeding shows in the same field, *A*, a slit-like gland in early regenerative phase, and two glands in which secretory activity is still in evidence. Note *B*, remnants of "ghost" surface epithelium, and *C*, absence of surface epithelium.

The literature suggests that the basic and best approach in therapy to irregular shedding is one of conservatism. A diagnostic curettage has been reported as relatively successful in treating the condition by removing the major portion of the functioning endometrium, that part of the endometrium susceptible to luteal influence. Subsequent to curettage no further evidence of the phenomenon was noted in several instances. Excessive estrogen exhibition, which theoretically would act to stimulate endometrial growth and to oppose the minor luteal influence by pituitary depression, has been reported as successful in controlling the bleeding from irregular shedding.[9]

A third method of treatment is to exhibit progesterone to the patient at a dosage level of 25 mg. a day for two or three days. This will rapidly and excessively produce luteal changes in the remaining endometrium, and, at the termination of progesterone exhibition, a relatively thorough and complete chemical curettage will take place. This form of therapy was first suggested by the experiments of Holmstrom and McLennan[9] and has been further supported by observations that in all instances where "break-through" bleeding occurred, and where the bleeding of irregular shedding was maintained for as long as twelve to sixteen days in our experimental patients, withdrawal bleeding occurred when the progesterone influence was ultimately removed from the patient. Once the diagnosis of irregular shedding of the endometrium is established by endometrial biopsy, excessive dosages of progesterone would be as rapid and as effective a means of controlling bleeding as any of the methods suggested to date.

Summary

A brief review of the literature concerning the phenomenon of irregular shedding of the endometrium has been presented. Menopausal women have been used in the experiments described as part of a long-range plan of sex hormone replacement in elderly women. In addition, they were used because of their potential primary role in the field of sex hormone bio-assay.

"Break-through" bleeding resulting from varied dosages of cyclic progesterone exhibition in uteri well-stimulated with estrogens has been described. In interpreting the "break-through" bleeding experiments, it became evident that irregular shedding of the endometrium could be produced by progesterone levels designed to simulate as closely as possible the usual course of the corpus-luteum phase of the normal menstrual cycle. Attempts to develop irregular shedding of the endometrium by producing "break-through" bleeding at low-dosage progesterone levels were relatively unsuccessful.

Biopsies were taken during the course of therapy on all patients, and representative sections have been presented and discussed.

The clinical administration of large dosages of progesterone has been suggested as a satisfactory method of therapy in dealing with established cases of irregular shedding of the endometrium.

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THE INCORPORATION OF THE ISTHMUS UTERI*

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THE isthmus uteri was first described definitively by Aschoff in 1905.[1] Since this time it has enjoyed a distinction equal in importance to that of the cervix and corpus uteri, having been defined as a structure entirely separate from both of these portions of the uterus and interposed between them. This designation of the isthmus as a separate entity served a worthy and useful purpose. Prior to the appearance of his article, the obstetrical literature abounded with the bitterest and most violent controversy concerning the origin of the lower uterine segment. Some of the articles are more than 100 pages long; many consist almost entirely of apparently purposeless diatribes directed at the champions of opposing theories. Aschoff's definition of the isthmus as a discrete structure brought instant order to this chaos, and supplied a plausible explanation for the derivation of the lower uterine segment. For this latter reason particularly, the concept of the isthmus uteri is considered a contribution of the first importance. Also, it focused attention upon a segment of the uterine mucosa which had received virtually no study before the appearance of this article, and, curiously, has received but little since. Frankl's paper,[2] which appeared in 1933, reviews the work done prior to that time and remains one of the most significant considerations of the subject. Although many gynecological texts have given only tacit approval to this concept, obstetrical thought has leaned upon it very heavily, particularly in an effort to explain the complex changes which occur in the uterus during pregnancy and labor.

Recently the concept of the isthmus as a well-defined and specific entity has been seriously questioned.[3, 4] The bases upon which the specificity of the isthmus was attacked were, first, that it is virtually impossible to measure the isthmus in terms of millimeters, as one should be able to do if the original definition were acceptable; second, that not only is the isthmus ill defined in any given uterus, but also in any collection of specimens it is extremely variable in length; third, the musculature of the isthmic segment is similar in structure to that of the corpus (this was also remarked upon by Demilin[5] in 1927); fourth, the isthmic musculature reacts anatomically to pregnancy in a manner precisely similar to that of the corpus; and finally, the isthmic segment can be reasonably hypothesized to form a functional unit with the corpus in labor. *These studies demonstrated the integrity of the isthmic segment and corpus as a functional unit, and*

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suggested that the designation of the isthmus as a separate entity was not only cumbersome, but actually misrepresented its essential function. However no information was given concerning the character of its mucosa, which, with a few notable exceptions,[6, 7, 8] has been almost uniformly represented as a peculiar and distinctive zone lying between the endometrium proper and the endocervix, and fundamentally different from both of them.

It is the purpose of this paper (a) to describe the histology of the isthmic mucous membrane, (b) to point out its essential similarity to the remainder of the endometrium, and, finally, on the basis of these findings, (c) to suggest that the concept of the isthmus as an entity separate from the corpus is no longer tenable. It is with reluctance that this conclusion is reached, for one of us has depended greatly upon this concept in the past. However, when the data to which allusion is made above are considered with that to be presented, it is concluded that the isthmus as we knew it is no more.

The isthmus uteri at present is depicted in the literature as lined by a mucous membrane which is thinner than that of the corpus. Its glands are described as similar to those of the corpus, but fewer in number and relatively refractory to the ovarian hormones.[2] The observation that these glands contain little or no glycogen in the luteal phase has been cited as proof that the isthmic mucosa is fundamentally different from the endometrium.[9] The stroma separating the glands is dense and is said to be rich in fibrous supporting tissue in contradistinction to the functional zone of the endometrium, which is more cellular and contains fewer fibrous tissue elements.[2] Also, the vascular supply of the isthmic mucosa is said to be composed only of short straight vessels of the type classified as II by Daron,[10] there being no coiled vessels of the type commonly seen in the endometrium.[11] When contemplating these stated characteristics of the isthmic mucosa, one is impressed that they bear more than a passing resemblance to the basal zone of the endometrium proper. It was with this similarity in mind that the present study was undertaken.

Materials and Methods

The material consisted of the following specimens:

(a) Thirty-eight human uteri removed at operation, fixed in the routine manner in Bouin's solution, and stained with hematoxylin and eosin. A large block of the cervix and isthmic segment, and a second block from the corpus proper were available for study. The endometrial cycles were distributed as follows:

Early follicular	6
Late follicular	12
Early luteal	6
Progravid	10
Post menopausal	4

(b) Twelve human uteri, surgically removed. Sections of the isthmic and corporeal mucous membrane were taken immediately, and placed in appropriate fixatives. The following stains were made: Hematoxylin and eosin, mucicarmine, Milligan's trichrome, iron hematoxylin (Heidenhain's), elastic tissue (by Weigert's method, counterstained with Van Gieson), glycogen (stained with Best's carmine after absolute alcohol fixation, and counterstained with Delafield's hematoxylin), and reticulum (by Wilder's silver method, counterstained with hematoxylin and eosin).

(c) Twelve pregnant uteri, certain details of which have been reported elsewhere.[3] This material was collected in 1941 and 1942 and after removal of the original blocks the remaining tissue was stored in 70 per cent alcohol after Bouin's fixation. Recuts from the stored material were made for the present study; the tissues cut nicely and the staining quality was excellent.

In each specimen the isthmic mucous membrane was compared with the endometrial basalis and with the functionalis.

Finally, the classical studies of Bartelmez,[12] O'Leary,[13] and Daron[10] have been so useful in the evaluation of these data that they may properly be listed among the materials.

Results

I. *Specimens From Nonpregnant Uteri.*—

In the examination of these specimens, it is not possible to delineate with certainty the point of transition from isthmic segment to endometrium proper. At an indefinite point the mucosa gradually becomes thinner as one approaches the cervix; in its upper reaches, then, the isthmic mucosa may be said to be indistinguishable from the rest of the endometrium. In the mid-portion, there are certain specific differences, the most important of these being that the mucosa is thinner, and that a true functionalis is lacking. Also, its entire thickness here shows a striking similarity to the basalis higher in the uterus. In its lower reaches, near the cervix, the glandular elements become more sparse. It is with the mid-portion of the isthmic segment particularly that the following descriptions are concerned.

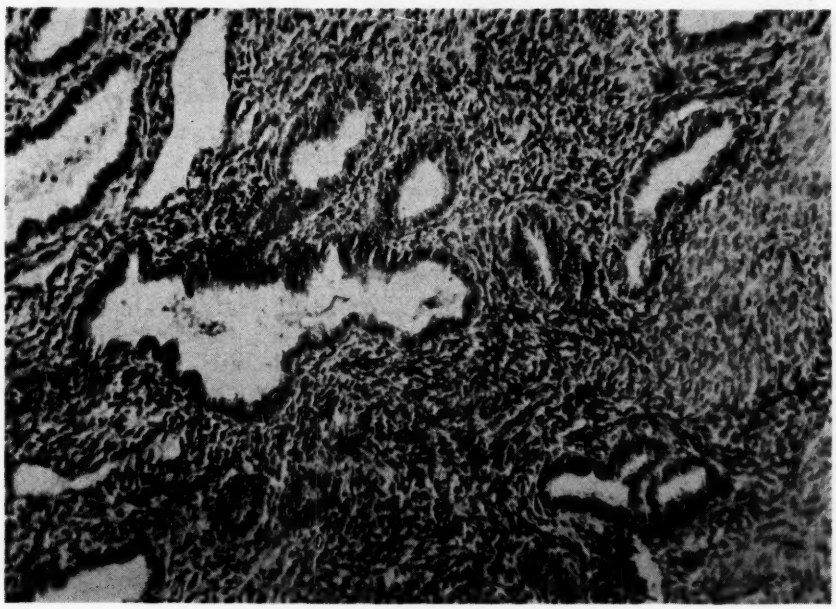

Fig. 1.—Basalis, luteal phase, showing serration of basilar glands.

A. *Glands.*—Irrespective of the stage of the menstrual cycle, in individual specimens the isthmic glands tend to conform in type to those of the endometrial basalis. They are somewhat more sparse than those of the basalis, and in most of the specimens, including those in the luteal phase of the cycle, they show only follicular effects. In some of the late luteal specimens, particularly those

obtained when the endometrial edema is maximum, the glands of the basalis are slightly irregular as though an effort at infolding were being made. *In occasional instances the superficial portions of both basalis and isthmic mucosa show distinct evidences of early secretory activity.* (It is of incidental interest that on casual examination of specimens of adenomyosis, the degree of secretory response here appears to parallel that which occurs in corresponding sections of the basalis and isthmic mucosa.)

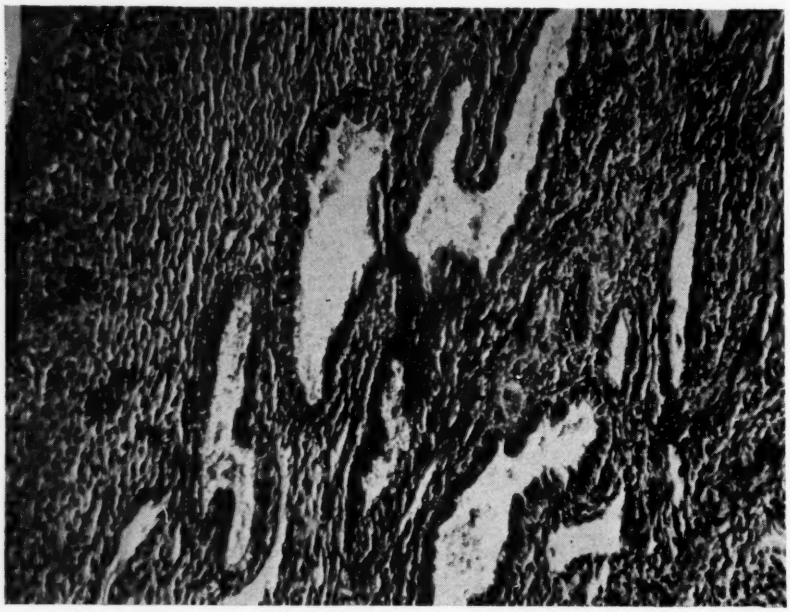

Fig. 2.—Isthmic mucous membrane, luteal phase, showing seration of glands.

B. *Stroma.*—The fundamental features of the stroma of basalis and isthmic segment are similar, although the latter appears in general to be somewhat less compact. The nuclei appear to be identical, but are less frequent in the isthmus; the areolar network is somewhat more dense in the basalis. Contrast stains show an abundance of fibrous tissue in both, this being considerably more than is found in the functionalis. No uniform pattern for elastic tissue was found, there being traces of this material scattered throughout. The reticular stains are of particular interest. A fine wavy network can be easily traced around each of the glands, merging into a complicated supporting network between the glands. The caliber of the reticular fibers is relatively thick, and the network dense, in both the basalis and the isthmic zone, and thinner and less compact in the functionalis. This is in agreement with Bartelmez' findings.[14]

In a few of the late luteal specimens scattered lymphocytes, plasma cells, and polymorphonuclear leucocytes may be found at random in the isthmic segment.

C. *Blood Vessels.*—It is recognized that isolated sections of endometrium give no true notion as to vascular pattern. However in studying these sections, it seems possible to identify without difficulty the short straight blood vessels described by Daron[10] which supply the basalis, and in the luteal specimens to identify the arterial fields of closely grouped tangentially and cross-sectioned vessels which characterize the coiled arterioles. Also, one notes what appear to be vessels which are intermediate between these. In occasional instances

coiled arterial fields can be seen in the endometrial basalis, but these are unusual and are particularly rare in the follicular specimens. In the isthmic segment, short straight blood vessels are also seen, though in general less frequently than in the basalis. Coiled arterial fields are extremely unusual in the follicular phase, *but in some of the luteal specimens groups of small but thick-walled blood vessels can be seen in the more superficial portions of the isthmic mucous membrane.* Whether these represent coiling as the result of the luteal influence cannot be stated. It seems not unreasonable that they do, for Markee[15] has demonstrated the possibility of transformation of straight arteries into coiled ones.

D. *Glycogen.*—The presence of glycogen in the glandular epithelium and lumina of the secretory functionalis is well known. Also, it has been shown[16, 17] that in many specimens it may be found in the follicular phase as well. Our findings are in agreement with this, the glycogen occurring in the *proliferative* specimens as small granules at the base of occasional glandular cells. None appeared in the lumina, nor was any demonstrated in any portion of either the basalis or isthmus. In the *secretory* specimens, the functionalis stained positively in the characteristic manner, the glycogen appearing as fine or coarse granules particularly in the luminal end of the cells and within the lumina. Glycogen granules were found very rarely in the stroma of the functionalis, as Spyker and Fidler[17] have pointed out. In the basalis, glycogen was found only semioccasionally in the glandular epithelium, and not at all in the lumina. When it did occur in the glandular epithelium, it was limited for the most part to the basal portion of a single cell of the gland, resembling in this respect the follicular phase of the functionalis. The *stroma* of the basalis was notable, however, in that considerable quantities of glycogen were diffusely scattered throughout. The findings in the isthmic segment were similar to those in the basalis, the stroma being generally rich in glycogen, and the glandular epithelium containing but little.

II. *Specimens From Pregnant Uteri.*—

In the specimens from pregnant uteri, where the isthmic segment is unfolded, and where the fetal membranes have come in contact with the isthmic mucous membrane, there is nothing to distinguish this thin and colorless mucosa from that of the endometrium proper. In the earlier specimens, however, where the isthmic segment is only partially unfolded, there is excellent opportunity to study the uninhibited growth of the isthmic mucosa. The decidua which is found here is comparable to that found higher in the corpus in those specimens where the uterine cavity is not obliterated by adherence of the reflected to the parietal decidua, being similar except that it is thinner in its lower reaches, that its glands are shorter and somewhat less numerous, that its blood vessels show definite evidence of coiling although their caliber is smaller, and that the features of the stroma are alike. In all of the specimens, the lowermost isthmic gland shows distinct gravid changes.

It is worthy of emphasis that in early pregnancy the luxuriance of the isthmic decidua appears to be related directly to the degree of apposition of the muscular walls of the isthmic segment. In other words: before six to eight weeks, where the anatomical internal os is still competent, definite, though incomplete pregnancy changes are present in the isthmic mucosa; immediately above the constricted zone a highly developed, typical decidua is present. In the specimens of about ten to fourteen weeks, when the reflected decidua is adherent to the parietalis and where the isthmic muscularis is beginning to dilate or "unfold" to receive the enlarging conceptus, the isthmic decidua may be extremely luxuriant, in fact much more so than in the endometrium proper where the pressure of the fetal membranes has reduced much of the mucosa to a colorless framework. In the former the three zones (compacta, spongiosa, and basalis)

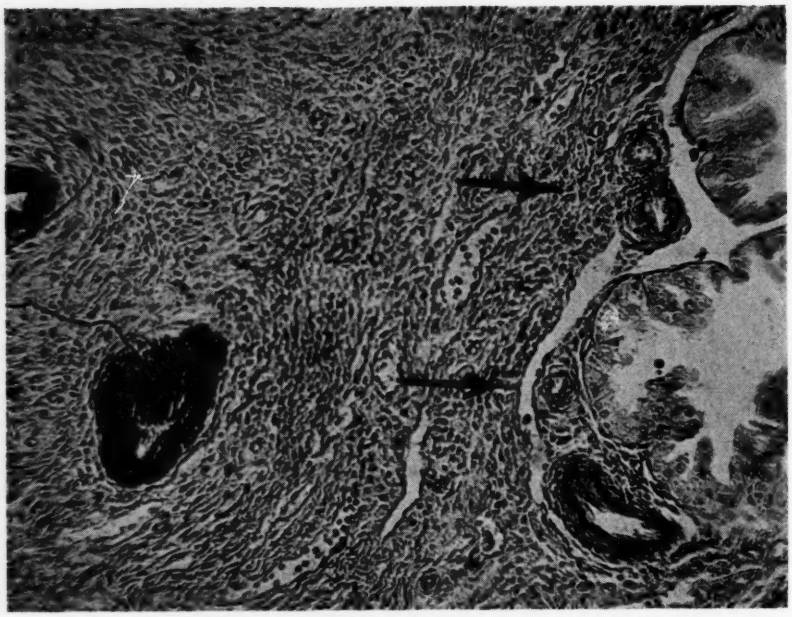

Fig. 3.—Pregnancy approximately ten weeks, Van Gieson stain. Cervical glands at left. Lowermost isthmic glands show well-marked pregnancy response, at right. Arrows indicate arterial field.

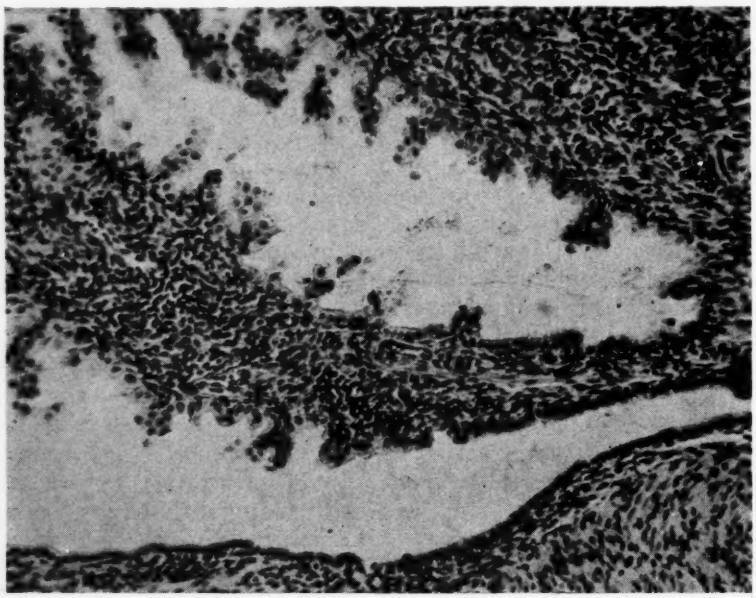

Fig. 4.—Isthmic mucous membrane, 8 weeks' pregnancy. Gland in lower portion of field shows distinct gravid changes at left, proliferative characteristics at right.

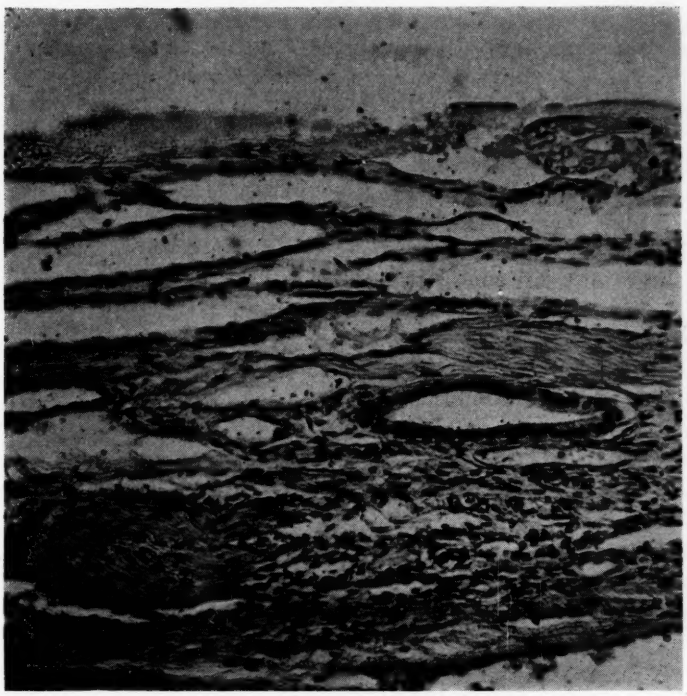

Fig. 5.—Four months' pregnancy. Section from mid-portion of corpus showing uterine cavity at top, lacey decidual framework mid-portion, and beneath this a gland which shows not the slightest response to pregnancy.

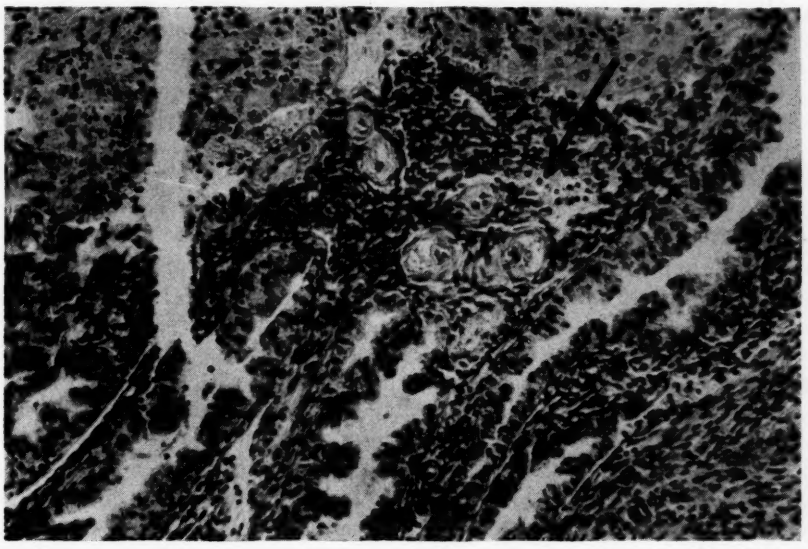

Fig. 6.—Isthmic portion two months' pregnant uterus. Coiled vessel in central portion of field (arrow).

are distinguishable without difficulty and are well developed. In one of our specimens the isthmic compacta shows sufficient excitement that it actually overhangs the upper cervical glands, drooping for a short distance into the cervical canal. Spongiosa and basalis are typical. After the sixteenth week. when the conceptus fills both corporeal and isthmic segments down to the level of the fibromuscular junction, there is little evidence in either segment of the lavish endometrial growth which characterized the first three months of pregnancy. Stieve has described this process as the "smoothing out" of the isthmus.[18]

Several arterial fields can be seen in the isthmic segments of all of the specimens of early pregnancy. In some of these elastic tissue is present in the blood vessels, while in others it is absent. One presumes from the characteristics of these fields that they are coiled arterioles. They resemble those which are seen higher in the endometrium, differing only in that the caliber is smaller and the walls slightly thinner.

The reticular pattern of this pregnant isthmic mucosa is similar to that of the remainder of the endometrium.

Comment

In the nonpregnant uterus. the isthmic mucous membrane has been shown to resemble in its essential features the basalis of the endometrium proper that is, the glands are similar in structure and react similarly in the follicular and corpus luteum phases of the cycle; the stroma between the glands is generally similar, in so far as hematoxylin and eosin, elastic tissue, trichrome, glycogen, and reticular stains reveal; the vascular patterns appear to be alike. It therefore seems reasonable to infer that the isthmic mucous membrane is not a distinct and autonomous entity, but rather that it is a continuation of the basalis of the endometrium proper. In its upper reaches it is indistinguishable from the basalis, while as the cervix is approached it becomes somewhat less differentiated. Since there is evident correlation, both quantitative and qualitative, in the pregnant uterus between the degree of decidual response and the amount of room available for such a response, the possibility arises that similar limitation of space in the nonpregnant state may preclude the development of a proper secretory reaction in this constricted zone. Certainly the uterine walls here are in close and rigid apposition, as is well known to anyone who has dilated this zone with the Hegar dilators. This calls to mind the relatively poor response of the lateral angles of the macaque endometrium[14]—here too there is limitation of space. When, in pregnancy of about three months, there is no physical impediment to growth, the isthmic mucosa appears to be just as capable of giving rise to a mature decidua as the mucosa higher in the corpus.

One must explain why the corporeal basalis does not show a full secretory response even in pregnancy; and similarly, why the differentiated basal zone of the pregnant isthmic mucosa also shows no apparent response to the progestational hormones. Two possibilities are suggested: first, that for indeterminate reasons this zone may be refractory to these hormones; second, and more likely, the short straight vessels which are believed to comprise the entire blood supply to the basalis may be incapable of bringing these hormones to this zone in great enough concentration to effect a secretory response.

Because of the findings presented here and elsewhere, it seems reasonable to reiterate the proposition made in the opening paragraphs of this paper, namely, that the concept of the isthmus as a specific entity, distinct from the corpus, should be interred after its many years of usefulness. The term "isthmus" must of course be retained; but its connotation should be analogous to that of the term "fundus uteri," namely, an integral part of the corpus.

Summary and Conclusions

Upon examination of routine preparations of nonpregnant and pregnant uteri, the isthmic mucous membrane is seen to be strikingly similar to the basalis of the endometrium proper. Special staining methods strengthen this similarity, and lead to the conclusion that the isthmic mucosa is a continuation of the basalis of the endometrium. The changes which both of these tissues undergo during the menstrual cycle and during early pregnancy are described.

In previous papers it was suggested that the corpus and isthmic segment should be considered a corporate unit, functionally and anatomically. The present study shows further similarity of these two portions of the uterus, and suggests a final respect in which the concept of the isthmus as an autonomous entity is untenable and should be discarded.

We are indebted to Miss Mildred Milligan, of the Gynecological Pathology laboratory of Northwestern University, who made the tissue preparations upon which this study is based.

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Discussion

DR. R. R. GREENE.—The authors have demonstrated that neither anatomically nor functionally is the isthmus uteri a separate entity or portion of the uterus comparable to the cervical and corporeal portions. It is, rather, a part of the corpus.

In October, 1946, Dr. Danforth presented to this Society the first part of the evidence on this subject. He showed that while the cervix is essentially of a fibrous nature, the isthmic portion of the uterus has a musculature similar to that of the rest of the corpus. During pregnancy, the individual muscle cells hypertrophy in a similar manner to those of the rest of the corpus. He demonstrated in a very convincing manner that after the third or fourth month it is not possible to distinguish microscopically between the isthmic and other portions of the corpus. He also showed that the isthmus becomes not only anatomically identical but also becomes a part of a single functional unit with the rest of the corpus.

This evening Drs. Danforth and Chapman have completed the interment of the isthmus uteri as a separate entity. Their evidence in this presentation has to do with the finer histologic details and evidences of function in the mucous membrane of this portion of the uterus. I have seen some of their microscopic presentations, and I can assure you that what they have told you is authentic. By routine and by special staining methods they have shown that the basic morphology of the isthmic mucous membrane is the same as the lower or basal portion of the endometrium elsewhere in the uterus. They have demonstrated that it shows the same minimal or inconstant response to the cyclic changes in hormone concentrations as does the basalis, and in pregnancy its functional response is such that it becomes identical to the endometrium proper.

Their evidence is complete. The obstetrical concept that the pregnant and parturitional uterus is made up of three separable and distinct portions (the corpus, the isthmus, and the cervix) should be changed to correspond with the facts. The isthmus is not a separate entity. It is a part of the corpus just as is the fundus a part of the corpus.

ABDOMINAL COMPLETE HYSTERECTOMY

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THIS presentation is a survey of the abdominal complete hysterectomies performed by the attending and resident staffs on the gynecological service of Passavant Memorial Hospital during the years 1929 to 1947, inclusive. Comparable series of cases have been previously reported comparing abdominal complete hysterectomy with supravaginal removal of the uterus, and abdominal hysterectomy with vaginal uterine extirpation. This review is an attempt to determine what, if anything, has been accomplished in the lowering of mortality and morbidity figures and in the reduction of complications and hospital-stay time as the result of changing attitudes regarding surgical procedures and postoperative care. Also what, if any, changes in mortality and morbidity rate have resulted from the use of chemotherapeutic and antibiotic agents. It has appeared of interest to compare in a general way this series of abdominal complete hysterectomies performed by a small group of operators, all of whom used essentially the same surgical technique and postoperative care, with reports of a somewhat similar character describing the results of vaginal hysterectomies. It is felt that such a comparison is pertinent because of certain widespread opinions held by the laity and by some within the profession. They consider that abdominal complete hysterectomy, even in the hands of competent gynecological surgeons carries with it a much greater risk than vaginal hysterectomy and that the abdominal approach is to be avoided in all instances except those in which it is extremely difficult or impossible to remove the uterus vaginally. We question the validity of these opinions because, as the result of this survey, it appears that abdominal complete hysterectomy for benign disease of the genitals need not be accompanied by notably higher mortality and morbidity rates than those which accompany vaginal hysterectomy.

Material

There are 1,034 abdominal complete hysterectomies performed for benign lesions of the genitals in this group. This series includes all operations in which the entire uterus was removed abdominally. Excluded are complete hysterectomies for pelvic malignancies, removal of the complete uterus at the time of cesarean section, and combined abdominovaginal operations. No attempt has been made to separate the series into different groups based on the simplicity of the procedure or on the clinical or pathologic diagnoses. In 449 instances the uterus alone was removed; in the remaining 585, additional abdominal procedures were performed. For comparison the cases are divided into three

groups: those operated upon from 1929 to 1937, those from 1937 to 1945, and those from 1945 to 1948. This grouping has been used because it roughly approximates the prechemotherapeutic, the chemotherapeutic (sulfonamide), and the antibiotic (penicillin) eras.

The pre- and postoperative management of the patient undergoing major gynecologic surgery on this service has changed materially during the two decades encompassed by this report. Certain basic procedures have, however, remained the same. Throughout the years the patient's general condition has been evaluated prior to operation and consultation with the medical services has been freely utilized. The preoperative medications have been essentially unchanged. Preoperative vaginal cleansing has always been routine but the intravesical instillation of methylene blue solution for the detection of minute bladder injuries has been used by the majority of the attending staff only since 1938. Cleansing of the abdominal skin has turned from iodine and alcohol to less stringent antiseptic solutions. The technique of the operation is not notably different now from that used in previous years. Abdominal exploration, coincidental appendectomy in appropriate cases, palpation to insure ureteral integrity, and the several steps in removal of the uterus and adnexa remain essentially the same. Lighter sutures are used more frequently today than in former years. Vaginal drains have not been used in the past ten years. Stay sutures were discarded prior to 1940.

During the first half of the time encompassed by this report blood transfusions were infrequently given and most patients received fluids by hypodermoclysis. In recent years all patients have had their blood typed prior to surgery and, if there is an evident anemia, compatible blood (of proper Rh type) is available in the operating room at the time of surgery. Intravenous fluids are begun in the operating room and are continued as seems necessary postoperatively.

Anesthesia has changed from ethylene and basal Avertin to cyclopropane or ethylene supplemented by intravenous curare. Pentothal inductions have recently been instituted. Spinal anesthesia has been rarely given.

Aside from the use of sulfonamides and antibiotics the most notable change which has taken place in the postoperative management of the gynecological patient has been the awareness of, and the active treatment of early thrombophlebitis and phlebothrombosis. Early postoperative ambulation has been stressed for many years but more patients are getting out of bed earlier today (on the second and third postoperative days) than formerly. In past years bed rest, hot fomentations, elevation of the affected leg and the application of leeches comprised the armamentarium for the care of fulminating thrombophlebitis. Today, the interns, residents, and attending staff are alert to the significance of minimal thigh and leg pains, positive Homan's sign, and unexplained modest temperature elevations. There is an insistence on the patient's carrying out passive and active arm, leg, and deep breathing exercises from the first postoperative day. The prophylactic administration of small doses of Dicumarol in amounts sufficient to lower prothrombin time to a level of approximately one-half normal appears to have been of value in aborting some of the suspected thrombotic processes. No venous ligations have been performed on any of the patients in this series.

Gentleness in the handling of abdominal viscera, added relaxation of the abdominal wall from properly administered anesthesia supplemented by curare, increased use of blood transfusions and the advent of the sulfonamides and antibiotics have reduced the incidence of abdominal distention and adynamic ileus to an almost nonexistent point. Gastric suction and colonic lavage have been rarely required after even the most extensive procedures since 1945.

Avoidance of overdistention of the bladder and removal of residual urine until the patient is able to empty her bladder spontaneously have always been practiced on this service. Prior to 1938, methenamine, the ketogenic diet, and bladder lavage were the measures used in caring for urinary tract problems. Sulfonamides and mandelic acid were given when their value became established. They are still used. Catheterization for bladder distress and catheterization for residual urine are still considered as important in avoiding serious upper urinary tract infections, today as they were twenty years ago.

Morbidity and Hospital Stay.—Dissatisfaction with commonly accepted rules for determining postoperative morbidity following gynecological operations has been frequently expressed. We are in accord with those who feel that the criteria for morbidity applied to postpartum patients (a temperature of 100.4° F. on any two days excluding the first twenty-four hours) is not properly applicable to postoperative gynecological patients. However, because this is the customary measure, it is the one which we have used in arriving at morbidity figures for the series of abdominal complete hysterectomies herewith reported (Table I).

TABLE 1

	NUMBER OF CASES	AVERAGE HOSPITAL DAYS	PER CENT PATIENTS MORBID	DEATHS	PER CENT MORTALITY
1929-1937	172	16.35	48.84	1	0.58
1937-1945	519	14.11	19.73	2	0.38
1945-1948	343	13.30	40.82	0	0.00
	1034	14.21	31.53	3	0.29

From 1929 to 1937, 172 abdominal complete hysterectomies were performed. The average hospital stay was 16.35 days. Of these, 84, or 48.84 per cent, were morbid according to the most used index. From 1937 to 1945, 519 complete hysterectomies were done. The average hospital stay was 14.11 days, with 103, or 19.73 per cent, morbid. It would probably have been felt that this sharp drop in morbidity after 1935 was due to improvement in postoperative care or to the use of chemotherapeutic agents had not the following years (1945-1948) shown a return to a morbidity rate of approximately 40 per cent. A diligent search of case records reveals nothing to explain the lower morbidity during the years 1937 to 1945. During the period 1945 to 1948, 343 abdominal complete hysterectomies were performed. The average hospital stay dropped to 13.30 days, with 140, or 40.82 per cent, of the patients classified as morbid.

The over-all morbidity rate for the 1,034 abdominal complete hysterectomies with 31.53 per cent with an average hospital stay of 14.21 days.

Although the average hospital stay now is three days less than fifteen years ago, the morbidity has decreased only 8 per cent. We believe that if we had used the morbidity curve devised by Jones and Doyle as an index there would have been a closer correlation between hospital stay and the morbidity rate.

While it is true that the over-all morbidity has not decreased notably since the advent of chemotherapeutic and antibiotic agents, the duration of the morbid course has been definitely shortened. Study of Fig. 1 will show that as many or more patients had a febrile course for two, three, or four days after 1937 as before that time. After four days, however, the morbidity percentage drops markedly and only one-fifth as many patients were morbid for seven days or longer in the 1945 to 1948 group as in those operated upon between 1929 and 1937.

Complications.—Certain complications may be expected to occur more frequently after abdominal complete than after either supravaginal or vaginal hysterectomy. Increased trauma to the pelvic veins during difficult or extensive dissections may be expected to increase the incidence of phlebothrombosis and thrombophlebitis in abdominal procedures. Concomitantly, more patients will have pulmonary complications. While the diagnosis and treatment of incipient thrombotic processes will reduce this incidence, the advent of chemotherapeutic and antibiotic agents have not, and probably will not, abolish the occurrence of vascular complications.

An abdominal complete hysterectomy uncomplicated by broad ligament, cul-de-sac, or adnexal pathology carries no more hazard to the ureter, bowel, and bladder than does a vaginal hysterectomy. Extirpation of the entire uterus with massively adherent benign broad ligament and adnexal processes is unavoidably accompanied by grave danger of injury to adjacent viscera. The incidence of such complications will vary with the difficulty of the procedure and the skill of the operator.

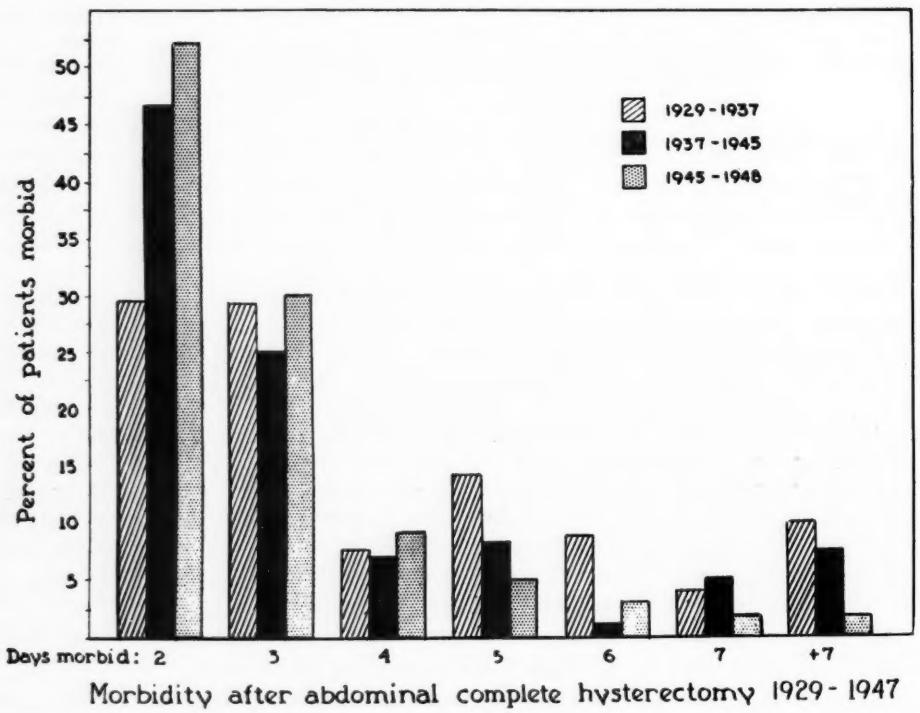


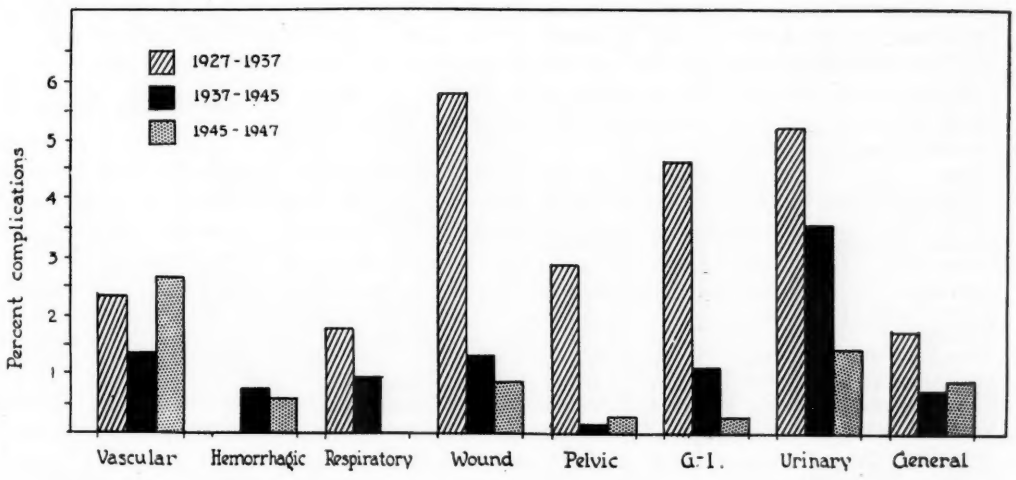
Fig. 1.

The unavoidable manipulation of, and trauma to, the abdominal viscera necessary in the freeing of extensive adhesions increases the likelihood of mechanical bowel obstruction and paralytic ileus. While the occurrence of mechanical obstruction will not be influenced by the use of sulfonamides or antibiotics, the gradual decrease in the incidence of ileus in this series (4.06 per cent in 1929-1937; 0.76 per cent in 1937-1945; 0.00 per cent in 1945-1948) is strong confirmatory evidence that ileus is, most often, a manifestation of peritoneal infection.

Serious abdominal wound infections decreased markedly in the past ten years. Prior to 1937, 5.8 per cent of the abdominal incisions after abdominal

complete hysterectomy were infected. During the years 1937 to 1945, the incidence decreased to 1.15 per cent. There has been but one serious wound infection in the last 343 cases. There was one evisceration in 1,034 operations.

Urinary tract infections are one of the major problems following pelvic surgery, whether that surgery is done vaginally or abdominally. There is no question as to what constitutes a pyelitis or a pyelonephritis, but the definition and diagnosis of postoperative cystitis is more elusive. Properly it should mean inflammation of the bladder, usually accompanied by pathogenic bacteria. It is our impression that unless urine cultures are done routinely, it is impossible to determine the exact incidence of cystitis. It has been customary on this service to make daily microscopic examinations of catheterized and residual urine specimens. For the purpose of this survey a diagnosis of "cystitis" has been made when there were ten or more leucocytes per high-power field of the microscope on more than one examination, and/or the patient complained of frequency and urgency and had a febrile course. The incidence of cystitis so defined is 1.44 per cent for the entire group. If the presence of ten or more leucocytes per high-power field of the microscope on one occasion is used as a criterion, the incidence of "cystitis" is 22.32 per cent for the 1,034 cases. (The percentages given may not be entirely accurate for the years 1941 to 1945 when less frequent urine analyses were done.)



Percent complications after abdominal complete hysterectomy 1929-1947

Fig. 2.

Table II details by groups (vascular, hemorrhagic, respiratory, wound, pelvic, gastrointestinal, urinary, general) the complications and their incidence which have occurred after 1,034 abdominal complete hysterectomies during the years 1929-1937, 1937-1945, and 1945-1948. No attempt will be made to discuss all of the complications recorded in Table II. It will be noted, however, that over the years there has been no decrease in the incidence of vascular or hemorrhagic complications. In all other groups since 1945 there has been a notable lessening in the incidence of postoperative problems (Fig. 2). Sinusitis, gastroenteritis, dermatitis, chicken pox, and paronychia should perhaps not be included since they are not postoperative complications per se. They prolonged the hospital stay of several patients, however, and are entered so that the record may be complete.

TABLE II. COMPLICATIONS AFTER 1,034 ABDOMINAL COMPLETE HYSTERECTOMIES

	NO. CASES	PER CENT INCIDENCE	1929-1937 172 CASES		1937-1945 519 CASES		1945-1948 343 CASES	
			NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Vascular.—								
Thrombophlebitis	11	1.000	2	1.16	5	0.96	4	1.16
Pulmonary embolism	5	0.480	2	1.16			3	0.87
Coronary occlusion	1	0.096					1	0.29
Fibrillation	1	0.096			1	0.192		
Vascular accident	2	0.192			1	1.192	1	0.29
Hemorrhage.—								
Intraperitoneal	1	0.096			1	0.192		
Vaginal vault	5	0.483			3	0.576	2	0.58
Respiratory.—								
Sinusitis	1	0.096			1	0.192		
Nasopharyngitis	1	0.096			1	0.192		
Pulmonary atelectasis	1	0.096	1	0.58				
Upper respiratory infection	1	0.096	1	0.58	1	0.192		
Pleurisy	1	0.096			1	0.192		
Pneumonia	2	0.192	1	0.58	1	0.192		
Wound.—								
Evisceration	1	0.096					1	0.29
Infected	17	1.450	10	5.82	6	1.152	1	0.29
Hematoma	1	0.096					1	0.29
Infected hematoma	1	0.096			1	0.192		
Pelvis.—								
Cellulitis	5	0.483	3	1.74	1	0.192	1	0.29
Abscess	2	0.192	2	1.16				
Gastrointestinal.—								
Ileus	11	1.056	7	4.06	4	0.768		
Mechanical obstruction	2	0.192			2	0.384		
Parotitis	1	0.096	1	0.58				
Gastroenteritis	1	0.096					1	0.29
Urinary.—								
Cystitis	15	1.440	3	1.74	11	2.112	1	0.29
Upper tract infection	3	0.280	1	0.58	1	0.192	1	0.29
Pyelitis	2	0.192	1	0.58			1	0.29
Prolonged residual urine	5	0.483			4	0.768	1	0.29
Urinary fistula	1	0.096	1	0.58				
Vesicovaginal fistula	1	0.096	1	0.58				
Ureteral fistula	1	0.096			1	0.192		
Incontinence	1	0.096	1	0.58				
Bladder infection	3	0.280			2	0.384	1	0.29
Nephritis	1	0.096	1	0.58				
General.—								
Low fever	1	0.096			1	0.192		
Shock	1	0.096			1	0.192		
Postoperative tetany	1	0.096			1	0.192		
Dermatitis	1	0.096	1	0.58				
Subphrenic abscess	1	0.096					1	0.29
Peritonitis	1	0.192	2	1.16				
Chicken pox	1	0.096					1	0.29
Paranephritic abscess	1	0.096			1	0.192		
Paronychia	2	0.096					1	0.29

Mortality.—There were three deaths in 1,034 abdominal complete hysterectomies (a mortality rate of 0.29 per cent) for benign uterine disease. Summarized case reports of these three cases follow.

CASE 1.—A 41-year-old white woman was admitted April 23, 1932. She complained of prolonged and increased menstrual bleeding for two months and a profuse vaginal discharge of many years' duration. She had had three normal labors and one miscarriage. The last

pregnancy was in 1922. A cervical and perineal repair had been done in 1928. The history was otherwise uneventful. Examination revealed a healthy-appearing woman, blood pressure, 140/90, temperature 98.4' F. There were no notable abnormal physical findings. The urine was negative. Red blood cells 4,250,000, hemoglobin 14.2 Gm. Pelvic examination showed a previously amputated cervix with a profuse endocervical discharge and a uterus containing multiple small tumors. A preoperative diagnosis of uterine fibromyomas was made. She was operated upon under ethylene and ether anesthesia on April 24, 1932. The operative findings were: an essentially normal upper abdomen; uterus twice normal size, containing small fibromyomas; tubes and ovaries normal. There were enormous varicose veins in the broad ligaments and perivaginal tissues. The cervix was pocketed due to the previous amputation. An abdominal complete hysterectomy was done. The operator noted that the procedure was extremely difficult because of the enormous varices. The appendix, uterine tubes, and ovaries were not removed. The first postoperative day the patient's condition was good. On the second day she had a severe chill followed by a temperature of 106° F. Chills and fever continued in a septic manner and she expired on the sixth postoperative day. An autopsy was performed and a generalized purulent peritonitis found.

CASE 2.—A 49-year-old white woman was admitted May 17, 1943. She had been under diabetic management (diet only, insulin not required) since 1929. A cholecystectomy had been performed five years previously. She was a nullipara. She complained of right lower quadrant pain, frequency and urgency of urination, and increased prolonged menstrual flow of four months' duration. Physical examination showed a well-nourished woman with blood pressure 168/98. General examination was negative except for an abdominopelvic mass about the size of a four months' pregnancy. Pelvic examination showed multiple uterine fibroids filling the pelvis and extending to the umbilicus. On admission the urine contained sugar (2 plus) and acetone (2 plus). She was placed on diabetic management by the medical service. The diabetes was brought under control and the medical service gave their consent for surgery on May 26, 1943. She was operated upon under ethylene and ether anesthesia. The operative findings were adhesions about the previous cholecystectomy site, the uterus contained several small fibromyomas and one large grapefruit-sized fibroid. The uterine tubes and ovaries were normal. An abdominal complete hysterectomy was done. At the beginning of the anesthesia the patient's blood pressure was 225/115. It rose to 250/120 and then dropped rapidly to 130/100. It gradually increased again to 190/110. The operative time was one hour and fifteen minutes. During the fascial closure respirations and heartbeat stopped for several minutes. Artificial respiration and respiratory stimulants successfully resuscitated her. When returned to her room she was cyanotic and had Cheyne-Stokes respiration; the pupils were unequal, the face asymmetrical. She did not regain consciousness and died fourteen hours after surgery, presumably of a cerebrovascular accident. Permission for autopsy could not be obtained.

CASE 3.—A 43-year-old white woman was admitted Dec. 29, 1944. She complained of prolonged excessive menstrual periods. She had had two normal pregnancies, the last in 1926. The history otherwise was not relevant. Physical examination was essentially negative except for an elevated blood pressure, 180/90. Pelvic examination showed the uterus to contain numerous large subserous and intramural tumors. A preoperative diagnosis of uterine fibromyomas was made. She was operated upon under ethylene and ether anesthesia. The operator noted that the liver and kidneys were negative. A fist-sized tumor of the right adrenal gland was palpated. The uterus contained multiple large fibromyomas. The tubes and ovaries were normal. An abdominal complete hysterectomy was done. The operating time was one hour and twenty minutes. It was not unduly difficult. At the beginning of the operation the patient's blood pressure was 220/120. During induction it rose to 250/140 and gradually fell thereafter to 200/110. She became cyanotic shortly after the fall in blood pressure and remained so. She was returned to her room. The opinion of the medical consultant was that she had suffered a cerebral accident. She died three hours after surgery. Permission for autopsy was not obtained.

In retrospect it would appear that a different surgical approach might have changed the result in one case—that in which the patient died of a diffuse peritonitis. However, the massive varicosities which made the abdominal procedure difficult would have rendered a vaginal operation equally so. Had she been operated upon during the last ten years, her chances of recovery from the peritonitis would have been immeasurably better because she would have received sulfonamides and antibiotics.

A mortality rate of 0.29 per cent for the series of abdominal complete hysterectomies compares favorably with the mortality rate of 2.4 per cent for the 41,050 abdominal hysterectomies collected by Campbell.

Comment

Comparisons between abdominal complete hysterectomy and supravaginal hysterectomy have been made repeatedly. Arguments have been voiced that complete removal of the uterus may be followed by shortening of the vagina, dyspareunia, premature menopause due to loss of ovarian function subsequent to a disturbance of a hypothetical uteroovarian relationship, and prolapse of the vaginal vault. The untenability of such objections to abdominal complete hysterectomy has been adequately demonstrated. The vaginal length in a properly performed abdominal complete hysterectomy is unchanged. Dyspareunia developing after an abdominal hysterectomy is the result of failure to support the ovaries properly or of too tense bringing together of the ligamentous supporting structures. Despite extensive laboratory investigations, there is as yet no definite proof that the uterus either elaborates a substance necessary for ovarian function or that a reciprocal relation with the ovary exists. That ovarian malfunction may result from failure to preserve ovarian circulation is unquestioned. A survey at present under way by one of us (J. W. H.) suggests that subjective symptoms of the menopause after total hysterectomy (vaginal and abdominal) occur in women with retained normal ovaries in about the same proportion and at about the same age as in a comparable healthy group not operated upon. None of the patients in this series have returned for repair of prolapse of the vaginal vault. This does not preclude the possibility that such a complication may have occurred and the patient gone elsewhere. However, during the eighteen years of this survey, the resident and attending staff do not recall any occurrence of vault prolapse after operation done on this service. Several prolapses of the cervical stump following supravaginal hysterectomy and enterocele after vaginal hysterectomy have occurred and the patients have returned for reoperation. It is reasonable, therefore, to assume that had there been any appreciable incidence of prolapse after abdominal complete hysterectomy, record or comment of it would have been made.

Discussions concerning the relative merits of abdominal and vaginal hysterectomy are perennial. It is unfortunate that the two procedures have, in some instances, been put upon a competitive basis for each has its indications and contraindications. There are certain broad rules with which most gynecologists, we are sure, will agree. Those patients with extensive pelvic endometriosis, with residues of chronic pelvic infection, large subvesical or broad ligament tumors, ovarian tumors of large size, and those with a tumorous fixed inaccessible uterus and a narrowed vaginal canal will, we suspect, be operated upon abdominally by even the most ardent advocates of vaginal hysterectomy. Likewise all of us will remove per vaginam unenlarged or modestly enlarged benignly pathologic uteri combined with uterine prolapse and vaginal herniations. Many operators will perform a vaginal hysterectomy on women who, although without notable vaginal relaxation, have an adequate vaginal canal and symptomatic small uterine or adnexal tumors which are almost certainly benign and mobile. The argument

appears confined, therefore, to the management of those patients who have massive benign tumors, those in whom there is reasonable question as to the nature of the pathology to be encountered, those who have had previous pelvic surgery which will complicate vaginal hysterectomy, those who, although possessing a snug nulliparous or virginal vaginal canal, nevertheless require removal of tumors of moderate size, and finally, those women who have any of the preceding and in addition have vaginal herniations requiring plastic repair. Some of us feel that most of the women in this last group will be best served by abdominal complete hysterectomy; others, in neighboring hospitals, sometimes in sister institutions, or on our own staffs, feel that vaginal hysterectomy is the procedure of choice for this group.

Among the reasons which have been cited for choosing vaginal in preference to abdominal complete hysterectomy are that vaginal hysterectomy carries a lower mortality rate, a lower morbidity rate, fewer complications, and that the postoperative patient is less uncomfortable. It is manifestly impossible to compare the amount of pain incurred by the two procedures for, in most instances, the more difficult cases, involving extensive dissection and increased trauma with resultant increased pain, are managed abdominally.

Comparison, however, of the abdominal complete hysterectomies reported herewith with that of a series of vaginal hysterectomies done by well-trained gynecologic surgeons at a neighboring institution (Presbyterian Hospital series reported in 1946 by Campbell) indicates that the mortality and morbidity rates for the abdominal complete and the vaginal hysterectomies are essentially the same, when performed by experienced operators or by a supervised residential staff. The Presbyterian report was specifically chosen for comparison because (1) the two services are geographically near to each other and draw from the same general population, (2) both institutions are similar in that they are part private, part free bed, (3) residential training is conducted under approximately the same type of attending supervision, and (4) Campbell's report was a carefully and accurately prepared analysis of the excellent vaginal work done on one of America's finest gynecological services.

Campbell reports a morbidity rate of 36.5 per cent for 2,798 vaginal hysterectomies as compared with a morbidity rate of 31.53 per cent for this series of 1,034 abdominal complete hysterectomies. The mortality rate for the Presbyterian cases was 0.214 per cent, for the Passavant cases 0.29 per cent. The hospital stay for the abdominal complete hysterectomies was 14.21, for the vaginal cases 12.25 days.

Certain complications were more frequent after the vaginal than after abdominal complete hysterectomies. Others were more common after the abdominal procedures. Apparently urinary tract infections are more frequent after the vaginal operation. However, as noted before, the criteria for a diagnosis of postoperative cystitis are not standardized and no comparison can, therefore, be properly drawn.

A comparison of Campbell's table of complications with the incidence of complications in Table II indicates that postoperative bleeding was twice as frequent and pelvic abscess was three times as common after the vaginal as after the abdominal procedures. On the other hand thrombophlebitis occurred ten times more often and pulmonary emboli were five times more frequent after abdominal than vaginal hysterectomies. Vesicovaginal fistulas occurred twice as frequently after vaginal hysterectomy as after abdominal complete hysterectomy. Differences in the incidence of intestinal obstruction and evisceration (not including prolapse of the uterine tube after vaginal hysterectomy) is figured in hundredths of a per cent.

Certain complications occurred after the abdominal procedures that were not present in the Presbyterian Hospital series. Commonest among them were wound infections, ileus, pelvic cellulitis, and prolonged residual urine. There is no doubt that, comparing the two groups, the complications were more numerous and the variety greater after abdominal complete than after vaginal hysterectomy. Despite this difference the mortality rates are essentially the same, the morbidity rate was slightly lower after the abdominal procedure, and there was but one plus day hospital stay more after abdominal complete hysterectomy.

Summary and Conclusions

This presentation is a report of 1,034 abdominal complete hysterectomies performed for benign pelvic disease during the years 1929 to 1947, inclusive. The cases have been arranged in three groups, corresponding to the prechemotherapeutic, the chemotherapeutic, and the antibiotic eras. Morbidity and mortality rates, the incidence of complications, and the hospital stay time have all been notably lowered as a result of changing attitudes regarding surgical procedures, postoperative care, and the advent of chemotherapeutic and antibiotic agents.

The over-all mortality rate was 0.29 per cent. One death occurred in the 172 cases operated upon prior to 1938 and two among 519 cases operated upon between 1938 and 1945. Two of these three deaths were due to cerebrovascular accidents. There were no deaths in the 343 cases operated upon after 1945.*

The number of patients morbid for seven or more days during 1945 to 1948 was but one-fifth the number during the years 1929 to 1937, although the over-all morbidity rate had been lowered only 8 per cent. The morbidity rate for the 1,034 cases operated upon between 1929 and 1947, inclusive, was 31.5 per cent.

There has been a marked decrease in respiratory, infectious, gastrointestinal, and urinary-tract complications during the past fifteen years. The incidence of vascular and hemorrhagic complications is essentially unchanged.

Abdominal complete hysterectomy for benign pelvic disease, performed by well-trained gynecologic surgeons, may now carry essentially the same mortality and morbidity hazard as vaginal hysterectomy. Such was not the case fifteen years ago when the vaginal approach was unquestionably safer. This change is the result of new attitudes relative to surgical and postoperative care, and to the advent of chemotherapeutic and antibiotic agents. Today there is little difference in the risks between the two methods of approach and the two operations need no longer be placed on a competitive basis because of presumed differences in surgical risk.

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*Not included in this report are 175 abdominal complete hysterectomies performed at Passavant Hospital between Jan. 1, 1948, and Jan 1, 1949. Including these with the 343 cases operated upon between Jan. 1, 1945, and Jan. 1, 1948, we can now report 516 consecutive abdominal complete hysterectomies with no deaths.

THE CERVIX IN PREGNANCY*

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THE cervix in pregnancy has not been given its due place in our obstetrical teaching. Most teachers have, during the past thirty years, to my knowledge, taught that the cervix is not to be exposed for inspection during pregnancy because the passage of a speculum and any cervical manipulation might lead to bleeding and abortion. Not only that, but a sort of defeatist attitude has been taken that nothing can be done about a cervical lesion during pregnancy, so why inspect the cervix. We have also taught that since early abortion occurs in about 12 per cent of cases, then the passage of any instrument into the vagina might easily lead the patient to conclude that her abortion was the direct result of the examination. Eleven textbooks of obstetrics of current issue have been reviewed and none of them states *specifically* that a speculum should be passed and the condition of the cervix noted. In fact, one well-known text states, "In private practice it is not necessary to examine the woman vaginally in the early months of pregnancy unless symptoms indicative of some abnormality occur." Another states, "In the early months of pregnancy, the vaginal examination, unless it is most gently done, may cause an abortion. For this reason the physician should limit his manipulations to those which are necessary to make the diagnosis of pregnancy and to rule out malposition of the uterus." Such teaching should be discontinued or modified, because the passage of a vaginal speculum carries with it no risk and it is quite necessary that we be thoroughly familiar with the patient's physical condition.

Many pregnant women have been kept in bed for days or even weeks and treated with expensive hormones when the bleeding was due to a cervical polyp or a cervical erosion. Women bleeding in late pregnancy have had diagnoses of placenta previa when polyps were furnishing the blood. An extensive cervical erosion present before conception may progress during pregnancy to the point where it begins to bleed. This teaching that the cervix is not to be inspected has probably retarded our knowledge of the various changes that occur in it during pregnancy. These changes are profound both macroscopically and microscopically. It behooves us all to attempt to acquire a more thorough knowledge of them as time goes on and to pass this knowledge on to our students. Experience is especially the best teacher when it comes to differential diagnosis.

Some of these changes seem to be related to carcinoma of the cervix later on and, as we all know, may constitute a malignant process even during the pregnancy. Various figures have been given, but combining many statistics it is estimated that carcinoma of the cervix occurs about once in 2,500 pregnancies. Certainly no one can deny that pregnancy does something to the cervix that

*Presented before the Chicago Gynecological Society, Nov. 18, 1948.

predisposes to cervical carcinoma. This fact has been brought out by many investigators and authors, but it is probably best presented by Wharton in his textbook, *Gynecology*. About 95 per cent of all cervical carcinomas have occurred in parous women, giving a ratio of parous to nonparous of 19 to 1. According to Raymond Pearl in his book *The Natural History of Population,* of every one hundred American women aged 45 years or over, 70 are parous and 30 are nonparous, or a ratio of only 2⅓ to 1. Putting these two figures together we can safely reason that cervical carcinoma is eight times as frequent in parous as in nonparous women. What then are these changes occurring in pregnancy and labor that may lead to malignancy later on? Can we not learn more about them by inspection as well as palpation; perhaps learn to prevent or correct some of them or learn to know which are carcinogenic, thus giving special attention to them as the patient grows older? These are challenging questions as yet unanswered and they call for serious consideration. Might we not begin by teaching routine and repeated inspection of the cervix during pregnancy and the puerperium? Examination of the cervix under good light and magnification both during pregnancy and at the time of the postpartum visits should be our duty and not just a flourish.

The macroscopic changes, of course, are in turn directly related to the microscopic, but tissue in vitro is never exactly the same as tissue in vivo because of the difference in their fluid content, temperature, circulation, and the various elements furnishing their color.

In pregnancy the most significant outstanding feature of the vaginal portion of the cervix visible through the speculum is its fluid content and the tension under which it seems to be, especially as the pregnancy advances. This is particularly true where lacerations from former deliveries have altered the circulation. This condition can never be fully appreciated through microscopic slides because of the loss of fluid and the chemical shrinkage that takes place in their preparation. However, the slightest injury can produce terrifying bleeding with the speculum in place, but since this blood is generally under only venous pressure or less, the removal of the speculum, allowing the surrounding tissue to collapse against the bleeding area, will generally lessen it markedly. A tampon is also much more effective at this time than it is when the cervix is firm. Nevertheless, due to the condition of the cervix in pregnancy, removing tissue for microscopic study is risky, as has been learned by experience, and the practice is therefore rather limited.

Several authors have advocated treating cervical erosion in pregnancy with the actual cautery, giving as their reason a profuse leucorrhea. Here it must be remembered that the pathologic organisms of the vagina should always be considered, including yeast and Trichomonas. Treating the vagina will many times improve the condition of the visible portion of the cervix. King and Touff treated forty-eight pregnant women with nonspecific cervicitis by radial cauterizations of the cervix and reported they had no abortions. This may be true, but they reported only 50 per cent were cured of the leucorrhea and they did not state what the resulting cervices looked like. On the other hand, such a procedure on a nonpregnant cervix will cure 90 per cent of such

erosions. The terms "leucorrhea" and "erosion," however, are not synonymous and in pregnancy it is doubtful if the term "erosion" should be used at all. The external os becomes everted due to its increased fluid content, the proliferation of the cervical mucosa, and the weight of the pregnant uterus. Miller, Martinez, and Hodgdon reported a series of 2,000 women in whom the cervix was cauterized during pregnancy, but again the question arises, why burn the cervix at any time just because it can be done? From experience one would say that the annoyance from the bleeding following a cauterization in pregnancy far offsets its therapeutic value. The resulting effect is not satisfactory.

From various parts of the world at various times has come the assertion that cervical lesions should be treated and an attempt made to sterilize the cervical canal and upper vagina during pregnancy, but, as a rule, if left alone, the vagina will be free of pathogenic bacteria. Conti and others in 1941 cultured the vaginas of 275 pregnant patients for various organisms. They made 275 aerobic cultures and 177 anaerobic cultures and 27 different organisms were found, 14.5 per cent of which were streptococci. They then followed these cases and had a gross puerperal morbidity of only 10.5 per cent. Six of the 28 morbid cases were extragenital. They came to the conclusion that erosions and mild, chronic, nonspecific cervicitis are not factors in puerperal morbidity, nor is previous cervical trauma. It would seem therefore, that once pregnancy has started we will not benefit the patient by attempting to treat cervical erosions and lacerations that are symptom free, even though these treatments do not cause abortion. If, however, the patient has an erosion that furnishes bloody show, then treatment is indicated; but in pregnancy it seems wiser to use caustic astringents rather than the cautery. A primipara, aged 34 years, began to have bloody show at seven months. She had had one treatment by cautery for a large cervical erosion before the pregnancy began. When a speculum was passed the bleeding was found to be coming from the surface of the eroded cervix. Negatol was applied to this surface several times and she then was free of bleeding the remainder of the pregnancy. Bloody show in pregnancy calls for careful investigation that should include visualization of the cervix.

I have never been able to appreciate to any great extent the value of palpation in the diagnosis of an early cervical carcinoma. We probably should continue to teach palpation, but certainly these days, when biopsy is being done more frequently, the Schiller test is available, smears are being studied, and magnification and lighting are better than they were, we will not discover many carcinomas of the cervix by palpation. A carcinoma that can be felt is generally a well-advanced malignant growth.

One of the most common lesions of the cervix in pregnancy is the polyp. Pregnancy seems to predispose to their development and I have had three patients who developed polyps during different pregnancies.

Mrs. W. E., aged 27 years, para i, gravida i, complained of spotting on May 4, 1935, when 3½ months pregnant and she was told to remain in bed for a while, which she did. Then at 6½ months, during her sixth visit following that, a pea-sized polyp of the cervix was discovered and removed with the actual cautery. She delivered three months later. During her second pregnancy two years later, at 8 months, she was symptom free, but a larger polyp than that described above was removed from the cervix in the same manner as the first. She had a spontaneous delivery seven weeks later. During her third pregnancy, eight years later, at 6 months' gestation, on May 17, 1945, she called and reported some bloody show. In view of her past history, she was told to come to the office. A very large and long polyp was hanging from the cervical canal and had begun to bleed.

I must confess the cervix had not been looked at for three and one-half months. This polyp, like the others, was removed with a cautery and she went about as usual and was symptom free. However, on Aug. 5, 1945, four weeks from term, she reported painless bleeding again and this time she was hospitalized. A sterile vaginal examination was made and no placenta was felt. A diagnosis of placenta previa was made, however, and she was kept in bed. She had some bleeding on and off but this became severe four weeks later in the middle of the night and she was delivered by cesarean section. The placenta bordered the internal os of the cervix and was situated on the posterior wall. She had a normal baby girl weighing 6 pounds, 5 ounces. This case illustrates five points: (1) cervical polyps are rather frequent in pregnancy; (2) all polyps do not bleed; (3) they may simulate placenta previa; (4) they can be removed with safety; and (5) painless bleeding in late pregnancy should always be considered evidence of placenta previa regardless of other findings such as polyps, if the bleeding is more than just a show.

Mrs. E., para i, aged 22 years, presented an interesting case of multiple verruca simplex thickly scattered over the upper vagina and the vaginal surface of the cervix. She was first seen when 2½ months pregnant. Biopsies were taken, the diagnosis established, and no treatment was given. She was cared for by another physician and was not seen again until eight weeks post partum and by that time all of her warts had disappeared.

TABLE I. MICROSCOPIC BIOPSIES

CASE	AGE IN YEARS	LENGTH OF GESTATION	PARITY	GLAND PROLIFERATION	PAPILLARY OUTGROWTHS	EDEMA AND VASCULARITY	INFLAMMATORY INFILTRATION	EPIDERMIZATION	DECIDUA
1.	30	2½ mo.	ii		+	+	++		
2.	28	8 mo.	i	+		+	+		++
3.	28	4½ mo.	ii	+			+		++
4.	35	2 mo.	ii	+	+	+	++		+
5.	37	6 mo.	iii	+	+	++	+		
6.	39	2 mo.	iii		+	+	++	+	
7.	22	3 mo.	i			+++		++	
8.	27	2 mo.	ii		++	++	+	+	+
9.	–	4 mo.	iv					CA.	
10.	43	5 mo.	iv					CA.	

The most common histologic changes found in the cervix during pregnancy have been listed by such authors as Fluhmann, Hofbauer, Stieve, and others and are as follows:

1. Edema and increased vascularity.
2. Inflammatory infiltration.
3. Hyperactive basal-cell layer and areas of epidermization.
4. Decidua.
5. Papillary outgrowths.
6. Proliferation of glands.

Fluhmann, in reporting 89 tissues removed from the cervix in pregnancy, thinks proliferation of glands is the most striking change found and makes the statement that the so-called cervical erosion of pregnancy is an adenomatous lesion rather than an erosion. I am inclined to agree, but it would seem that the increase in fluid in the tissues as described under gross descriptions may furnish some misinterpretation here. What may seem like proliferation can be a crowding of glands due to fluid loss in preparation. As stated before, the microscopic picture of this tissue is not always the true one because of the changes that occur between its procurement and its ultimate staining. There

is, however, considerable proliferation and the question arises, is it this change, together with others accompanying it, that lays the groundwork for a malignant change later?

Epidermization was found in only two of the ten biopsies, but here no interpretation can be made from such small areas. Carmichael and Jeaffreson found areas of atypical multilayered epithelium in 137 out of 334 cervices removed at operation, or an incidence of 41 per cent. One of their statements I quote:

"Epithelium that is undergoing atypical proliferation is probably more apt to become malignant. Reproduction and disease probably have little effect on the incidence. Endocervical epithelium can undergo a process of gradual metaplastic transformation into squamous epithelium, losing its function of secreting mucin, and assuming that of storing glycogen; it is thus transformed both in function and structure."

The question arises, can this metaplastic transformation go the other way, from squamous-cell nests, or nests of indifferent cells that have remained planted under the secreting columnar cells taking on a secretory function? Novak thinks it cannot. Does squamous epithelium always push glandular epithelium out and away? These questions cannot be answered at present, nor can the influence of pregnancy on the areas be established. Pregnancy probably is not related in any way to this finding, because Carmichael and Jeaffreson's incidence was 35 per cent for women under 50 years, compared with 50 per cent when over that age.

Decidua was found in four out of ten, and here again no explanation can be made. As a rule it is never solid, but in quite discreet patches at times, and also may constitute only a few neighboring cells here and there. It apparently is by no means a constant finding in this part of the cervix during pregnancy. Ectopic decidua seems to be found in redundant tissue more often than in the main structure. Where there are papillary outgrowths into the cervical canal, three of these papillae may be filled with leucocytes, round cells, and plasma cells, and the fourth may be solid decidua formation covered intact with columnar epithelium.

A common finding in these ten biopsies is infection, especially if one considers the papillary outgrowths, all of which are generally infected when found here, whether the patient is pregnant or not. Other authors, however, eliminate these small infected papillae from their statistics and it would seem that extensive cervicitis connected with this proliferation, eversion, or erosion, as one may wish to call it, is not the predominating lesion.

Summary

Visualization of the cervix should be used as a part of our prenatal care.

Bloody show in pregnancy calls for inspection of the cervix in many cases and in the past has not been used enough.

Our knowledge of the changes occurring in the cervix during pregnancy is very limited and less is known about the gross pathological changes than the microscopic.

There is apparently some relationship between parturition and cervical carcinoma. We must, therefore, acquire the knowledge to explain this relationship, and repeated inspection of the cervix together with biopsy when indicated should promote this learning.

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636 CHURCH STREET.

VULVOVAGINAL MONILIASIS

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YEAST vulvovaginitis comprises the common form and the most frequently occurring mycotic infection in the genital region. The vulvar disease cannot be separated from the vaginal involvement, for it usually does not persist unless fed from a vaginal focus. Numerous studies have been reported concerning the incidence of Monilia in the lower genital tract in both pregnant and nonpregnant women with and without subjective symptoms.[1-9] It is difficult to come to any conclusions concerning incidence because of the variety of ways in which these studies have been set up. However, generally speaking, it is thought that about 10 per cent of the female population at large harbor yeast, the majority of whom are asymptomatic. Of those patients presenting themselves to the gynecologist complaining of vaginal discharge and pruritus, it has been reported that about 20 per cent are found to have Monilia. In 40 to 45 per cent of all pregnant women the organisms are found in the vaginal cultures, and about 10 per cent of these cause symptoms.

Monilia albicans (Candida albicans) is by far the most common organism responsible for yeast vulvovaginitis. The diagnosis is dependent upon the demonstration of the organisms. Clinically this is accomplished by microscopic examination of a suspension of the vaginal secretions. The fungus appears as a woven mycelium of long, branched filaments of hyphae; occasionally buds may be seen arising from the stems (Fig. 1).

Material

After reviewing the literature on this subject a clinical laboratory investigation was carried out to determine the incidence of yeast vulvovaginitis. Vaginal exudate was removed from a series of women presenting themselves to the Gynecology Out-Patient Department of the University Hospital. No selection of cases was made, but whenever it was possible specimens were removed and transferred to culture tubes. This investigation was carried out on 836 patients who were seen in the clinic during a two and one-half month period.

Each patient included in this study was questioned as to whether she had had any symptoms which might be attributed to vulvovaginitis. Careful questioning was done to elicit a history of vulvar or vaginal pruritus, burning, ulceration, erythema, swelling, or other irritative phenomena. The patient was also asked if she had a vaginal discharge; this, being a subjective impression, was compared with the objective evaluation of the examiner as to whether there was an *abnormal* vaginal exudate (other than mucus and desquamated epithelial

cells normally found in the lower reproductive tract). All of the data so obtained were placed on a large chart immediately after the examination and the culture tube inoculated from that patient was given a number for future identification.

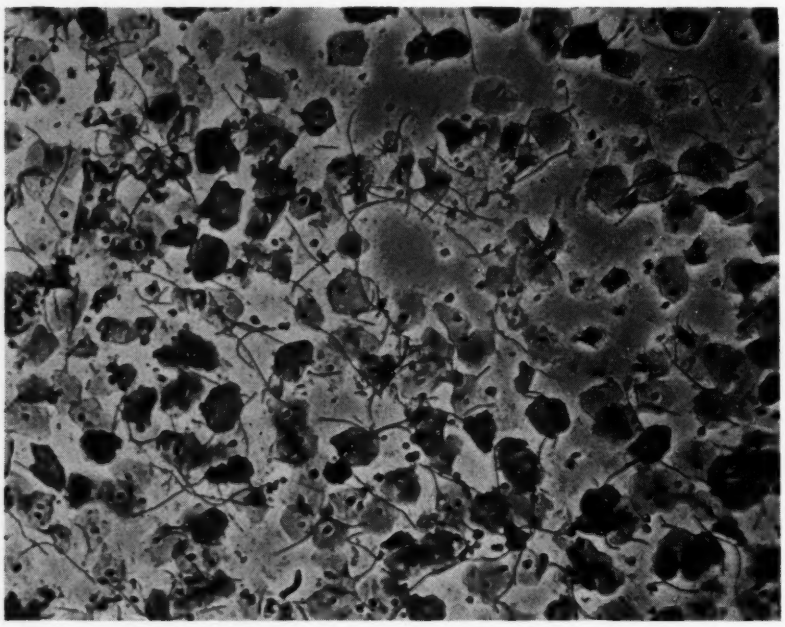

Fig. 1.—Mycelia of *Monilia albicans* seen on suspension of vaginal exudate. Silver carbonate stain. (×100.)

Certain other facts about the patients were noted on the data chart. If they were known diabetics, pregnant, or had leucoplakia or other conditions that might be related to vulvovaginitis, this was so recorded in an attempt to correlate culture results with various clinical findings. With this series of over 800 cases it was hoped that any correlation that might be present between the patients' signs and symptoms and the actual (culture-proved) existence of vaginal mycosis could be demonstrated; or, conversely, it could be shown that no such relationship exists. It was also hoped we might determine how often actual mycotic infestation caused clinical symptoms or recognizable pathology, and what was the relative reliability of microscopic examination of a suspension of vaginal exudate as compared with culture methods in demonstrating the existence of yeast organisms. These and other questions presented themselves as problems about which information could be gained by such a study as this.

An attempt was made to skin test these patients for Oidiomycin sensitivity (therefore, present or previous yeast infestation) but because of the nature of the clinic practice this was found to be impractical. The chief difficulty along this line was in getting the patients back in twenty-four to forty-eight hours for evaluation of the test, as most of them returned to their homes (often hundreds of miles away) shortly after their gynecological consultation.

Speculum examination was carried out prior to bimanual pelvic palpation. A lightly lubricated (K-Y Jelly) speculum was introduced into the vagina and two specimens of the exudate found therein were removed by two sterile wire loops. Each loop then inoculated the culture tube slant in two places, thus giving several separate inoculations of the culture medium. These inoculated tubes were kept at room temperature (68 to 72° F.) under aerobic conditions

for from four to eleven days. At the end of this time they were examined for the presence of bacterial or yeast growth. Sabouraud's medium containing 15 units of penicillin per cubic centimeter was used. It was slanted in 6 by 1 inch culture tubes, using approximately ten cubic centimeters of medium in each tube.

When growth was observed in the culture tube its gross characteristics were noted and correlated with the microscopic findings after making a suspension of the organisms and staining it with gentian violet or methylene blue. After becoming thoroughly familiar with the culture characteristics of the commonly found organisms the procedure of making microscopic examination on stained smears was carried out only when doubt existed as to the true nature of the growing organism.

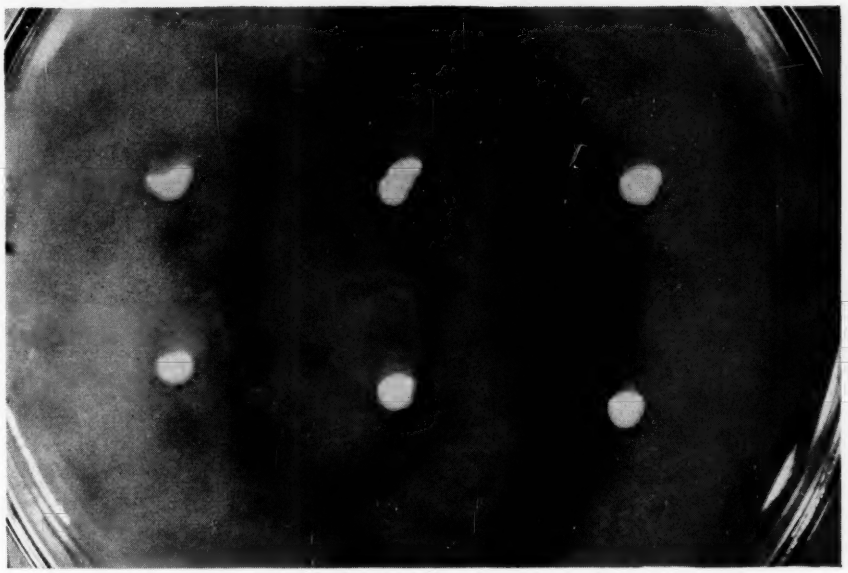

Fig. 2.—*Monilia albicans* cultured on Sabouraud's medium.

In studying the organisms that grew under these circumstances it was found that four different cultures made their appearance with relative consistency:

1. A white, scalloped-edged, smooth-surfaced, dry colony (Fig. 2) which on microscopic examination was made up of *Monilia albicans* organisms primarily in the budding form (Fig. 3). When the colony is over 5 days of age it forms a brownish central crust.

2. A white, rough-edged, dry, rough-surfaced colony (Fig. 4) with a tan, wormlike building up of the central surface. This showed on microscopic examination an organism with arthrospores and was identified by Dr. E. Cawley of the Dermatology Department as Mycoderma (Fig. 5).

3. A red, smooth-edged, glistening, smooth-surfaced colony which on microscopic examination showed a yeastlike budding organism with a gelatinous capsule but no mycelial forms. This was identified as a red Torula (Cryptococcus).

4. A gray, smooth, irregular-edged, moist, mucoid, flat-surfaced colony which on microscopic examination showed short, fat, encapsulated bacilli which tended to form short chains. This was identified as a nonspecific bacterium found commonly as a saprophyte on mucous membrane surfaces.

The cultural characteristics of these organisms were constant, and after a short time it was generally easy to recognize the organism by gross observation of the culture tube. It is also interesting to note that the Monilia and Mycoderma organisms had a typical "brewery" or "bakery" odor, while the bacteria and Torula were completely lacking in odor. A small number of the tubes became contaminated by common airborne molds (Aspergillus).

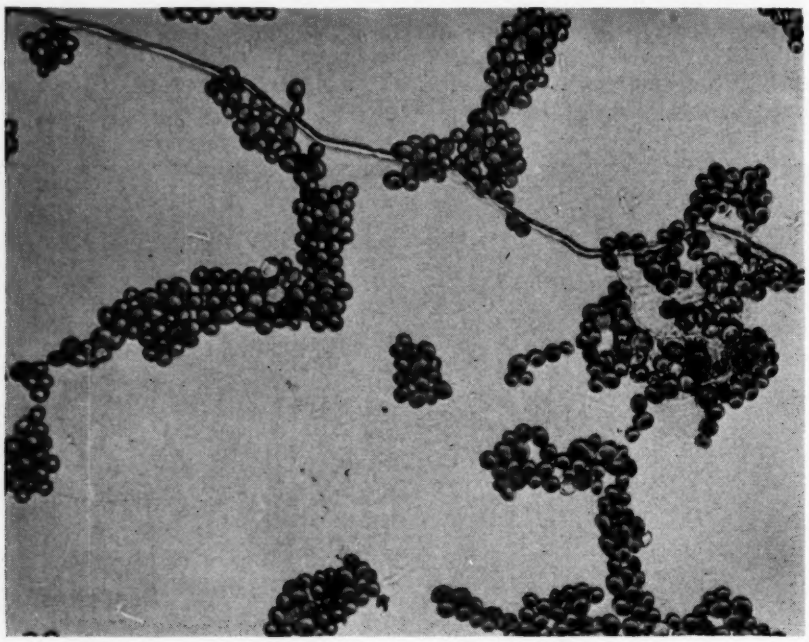

Fig. 3.—Photomicrograph of Monilia albicans. Suspension made from colony seen in Fig. 2 and stained with methylene blue. (×450.)

Other bacterial flora which one might expect to encounter in vaginal secretions were apparently prevented from growth by the nature of the medium and/or the added penicillin. In all cases where objective clinical findings were such as to indicate the presence of a vulvovaginitis a wet-drop suspension of the vaginal exudate was examined for yeast mycelia and active trichomonal organisms. It should be remembered the *Monilia albicans* in vivo produces predominately a mycelian moldlike growth while in vitro it assumes predominately a budding, yeastlike form except in old cultures wherein the mycelia increase in number. It has also been previously shown that the *Monilia albicans* is the only commonly found Monilia in man that is pathogenic to him.

In evaluating the statistical results of this study it was found that of the 836 patients cultured 166 developed yeastlike growth and 122 produced bacterial growth (Table I). Of the 166 cases which were positive for yeastlike organisms 123 showed *Monilia albicans* alone, 10 *Monilia albicans* plus Mycoderma or the red Torula, 10 *Mycoderma* alone, 20 the red Torula alone, and 3 a combination of Mycoderma and the red Torula. Of the 122 positive cultures of bacteria, 17 were found in conjunction with a yeastlike growth and 105 without. Thus, in the 836 patients cultured there was an incidence of 19.9 per cent positive yeastlike growth (Table II) and 14.6 per cent bacterial growth. Of the entire series of patients, 15.9 per cent had *Monilia albicans,* 1.8 per cent Mycoderma, and 3.7 per cent the red Torula.

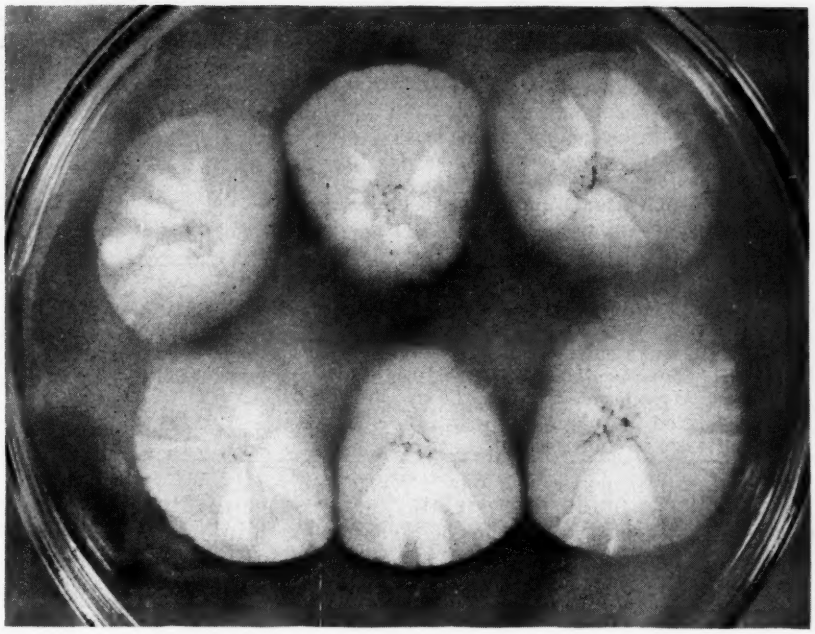

Fig. 4.—Mycoderma cultured on Sabouraud's medium. Inoculate obtained from vaginal exudate.

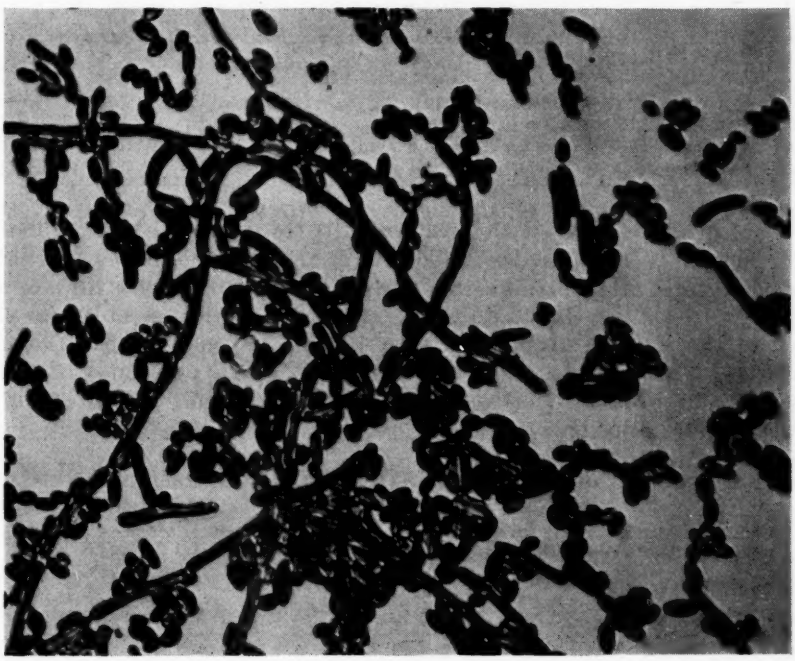

Fig. 5.—Photomicrograph of Mycoderma. Suspension made from colony seen in Fig. 4. Methylene blue stain. (×450.)

TABLE I. INCIDENCE OF POSITIVE CULTURES

A. Number of patients cultured	836
B. Number of cultures developing yeastlike growth	166
1. *Monilia albicans* (alone)	123
2. Mycoderma (alone)	10
3. Red Torula (alone)	20
4. *Monilia albicans* and Mycoderma	2
5. *Monilia albicans* and Red Torula	8
6. Mycoderma and Red Torula	3
C. Number of cultures developing bacterial growth	122
1. Bacteria (alone)	105
2. Bacteria and yeastlike growth (included above)	17

TABLE II. TOTAL INCIDENCE OF VARIOUS ORGANISMS CULTURED

A. Yeastlike cultures	166	(19.9%)
1. *Monilia albicans*	133	(15.9%)
2. Mycoderma	15	(1.8%)
3. Red Torula	31	(3.7%)
B. Bacterial cultures	122	(14.6%)

An attempt was made to correlate the presence of Monilia, other yeastlike organisms and bacteria with the occurrence of clinical signs and symptoms attributable to a vulvovaginitis. In the study group as a whole (836 patients), 182 (21.8 per cent) had subjective symptoms of vulvovaginal irritation, and 216 (25.9 per cent) stated they had a vaginal discharge (Table III). It was determined that 192 (22.9 per cent) of these 836 patients objectively had an abnormal vaginal exudate. Thus, about one-third (37.0 per cent) had one or more sign or symptom usually attributable to a vulvovaginitis.

TABLE III. PATIENTS WITH CLINICAL SIGNS AND SYMPTOMS SUGGESTIVE OF VULVOVAGINITIS

A. Subjective symptomatology:		
1. Irritation (pruritus, burning, pain, etc.)	182	(21.8%)
2. Subjective vaginal discharge	216	(25.9%)
B. Objective abnormal vaginal exudate	192	(22.9%)
C. Incidence of one or more sign or symptom	309	(37.0%)
D. Total number of cases without signs or symptoms	527	(63.0%)

The group of patients with positive cultures of yeastlike organisms or bacteria was similarly evaluated (Table IV). Of the 133 patients with positive cultures of *Monilia albicans*, 51 (38.3 per cent) presented signs and/or symptoms of vulvovaginitis. The 15 cases with positive Mycoderma cultures showed an incidence of the same clinical picture in 4 (26.7 per cent). Red Torula apparently "caused" these signs and symptoms in 12 (38.7 per cent) of the 31 cases, and the bacteria were associated with clinical signs and symptoms in 37 (30.3 per cent) of the 122 positive cultures.

TABLE IV. INCIDENCE OF SIGNS AND/OR SYMPTOMS OF VULVOVAGINITIS IN CASES WITH POSITIVE CULTURES

A. *Monilia albicans*	51	(38.3%)
B. Mycoderma	4	(26.7%)
C. Red Torula	12	(38.7%)
D. Bacteria	37	(30.3%)

Summary

A brief review of the literature pertaining to yeast vulvovaginitis was carried out. Following this a clinical-laboratory investigation was undertaken,

studying 836 consecutive gynecological outpatients. The primary purpose was to gain information as to the incidence of vaginal yeast and the relationship to symptoms usually ascribed to it. It is commonly taught that in the production of bloodless, irritating vaginal discharge moniliasis ranks after Trichomonas vaginitis and cervical erosion, in that order.

In this study it was found that 15.9 per cent of the patients coming to a gynecology clinic harbor *Monilia albicans*. Of these, 38.3 per cent presented symptoms and/or signs that might be attributed to a yeast vulvovaginitis. However, when the study group was considered in its entirety, 37.0 per cent demonstrated the same clinical findings. In addition, it was shown that the patients from whom Mycoderma or the red Torula were cultured exhibited the same picture, with an incidence of 26.7 per cent and 38.7 per cent, respectively. This contributes to the opinion the vulvovaginal pruritus, pain, burning, swelling, and the complaint of vaginal discharge, as well as the objective finding of what might be considered an abnormal vaginal discharge, cannot be accurately correlated with the laboratory demonstration by suspension or culture of the presence of yeast. Conversely, the proved presence of vulvovaginal Monilia does not call forth the above-mentioned clinical findings any more frequently than were found in this study group at large. In fact, 61.7 per cent of the patients proved to harbor *Monilia albicans* exhibited no signs or symptoms of vulvovaginitis.

It was possible in two patients in whom yeast infection was suspected to demonstrate mycelia and yeast forms on wet suspension, but a positive culture was not obtained. On the other hand, cultures often confirmed the diagnosis made on wet suspension and frequently showed the existence of yeast when its presence was unsuspected. The culture method is presented as a simple procedure for demonstrating the presence of vulvovaginal yeast when one is led to suspect its presence as a cause for an irritating bloodless vaginal discharge.

Photographs are shown to demonstrate some of the organisms commonly obtained by this culture method. Figs. 1, 2, and 3 show *Monilia albicans* in vivo, cultured on Sabouraud's medium and a photomicrograph of the organism in vitro. Figs. 4 and 5 show in vitro Mycoderma culture and microscopic characteristics. The red Torula is easily recognized by the culture characteristics (including its red color) and the absence of mycelia in stained preparations of the organism when examined microscopically. The bacteria can be readily differentiated from the yeastlike organisms.

If when dealing with an irritating vaginal discharge and a secondary vulvitis one is unable to demonstrate other causes, i.e., *Trichomonas vaginalis,* endocervicitis, cervical erosion, senile vaginitis, gonorrhea, etc., and mycelia and yeast forms do not appear on wet suspension of the secretions or skin scrapings, it is deemed advisable to instigate culture studies as outlined above. If in such a case the cultures show *Monilia albicans* one has a scientific basis on which specific therapy can be instituted.

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PREGNANCY AND THE ADOLESCENT*

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THE frequency with which the young primigravida has presented herself for obstetric care at the Gallinger Municipal Hospital of Washington has been impressive and in a sense unique. Whenever the occasion arose for a discussion of our experiences with this particular group of patients, statements both in agreement and in contradiction would be made among us based only on impressions. Most textbooks of obstetrics have treated this subject briefly, if at all. References in the more recent literature are few, and it semed to us that some of the observations, as well as the conclusions drawn from them, were made from too small a number of cases. Schmitz and Towne[1] have already stated that the young primigravida receives little attention in our present-day texts.

These circumstances prompted us to make an analysis of our own patients between the ages of 12 and 16 years, inclusive. It will become evident that the information that will be presented from this study cannot be entirely applied to other locales because of the character and the social and economic status of our patients. There are some observations, however, that should prove to be of value in any consideration of the very young mother.

Material

At the Gallinger Municipal Hospital there were 10,699 deliveries during the three-year span including 1945, 1946, and 1947. This study is based on an analysis of 634 young mothers, 16 years of age or under, who were delivered in the corresponding period of time. On the basis of these figures one arrives at an incidence of 6.3 per cent (see Table I) or a ratio of 1:17.

TABLE I. INCIDENCE, 6.3 PER CENT

YEAR	DELIVERIES	YOUNG
1945	2,432	161
1946	3,421	180
1947	4,816	293
Total	10,669	634

The age distribution is indicated in Table II. A little over half of them were 16 years old. The mean age of the entire group is 15.4 years.

Since the patients admitted to the Obstetric Department at Gallinger are predominantly Negroes, it was not surprising to learn that almost 99 per cent of the young mothers in our series were Negroes. This homogeneous factor may well be considered an advantage in this survey. There were only seven white young primigravidas; two of them curiously enough were 12, one was 14, and four were 16 years of age.

*Presented at a meeting of the Texas Association of Obstetricians and Gynecologists at Houston, Nov. 17, 1948.

An analysis of the marital status of these young girls showed that only 96, or 15 per cent, of them were married.

TABLE II. AGE DISTRIBUTION

AGE (YEARS)	NO. OF CASES	PER CENT
12	3	0.5
13	19	3.0
14	77	12.1
15	163	25.7
16	372	58.7
Total	634	100.0

Prenatal care was considered generally good or adequate. Only 34 of them, or 5.3 per cent, had no antepartum care. It is suspected that the age and unwed state of these patients, in addition to eliminating the suspense of the diagnosis of pregnancy as soon as possible, becomes the immediate concern of their mothers, so that prompt and early obstetric care is sought for their pregnant young daughters.

All of the adolescents in this series were not primigravidas. There were 39 of them who were delivered of their second babies; one was 14, 6 were 15, and 32 were 16 years of age. In addition, there was one mother in the 16-year-old group who was delivered of her third baby. Thus, all but 40, or 93.7 per cent, were primigravidas (Table III).

TABLE III. PARITY

AGE (YEARS)	PARA 0	PARA I	PARA II
12	3		
13	19		
14	76	1	
15	157	6	
16	339	32	1
Total	594	39	1
Primigravidas—93.7%			

Antepartum Course

During the antepartum course, it is only on the major maternal complications that we wish to focus our attention. Table IV shows that in our series one-third of the patients departed from the average uncomplicated antepartum course. Should the purely obstetrical causes be examined alone, then it is found that the toxemias, premature separation of the normally implanted placenta, and placenta previa involve a little over one-fifth (21.3 per cent) of these young mothers. That the toxemias are the most frequent and the most important complication, we are in agreement. It is noted that in our experience they constituted a little less than 20 per cent of the adventitious circumstances altering the normal course of pregnancy. It is to be further noted that of the 211 listed complications the toxemias comprised 60 per cent of them.

It is significant that a definite relationship seems to have been established between the ages of our young mothers and the frequency of the toxemias. From Table V it can be deduced that the younger the mother, the higher the incidence of the toxemias.

Of the 125 instances of this complication, almost three-fourths of them (73.6 per cent) were classified as mild pre-eclampsia, about one-fifth of them (20.8 per cent) as severe pre-eclampsia, while seven cases (5.6 per cent) were eclampsia (see Table VI).

A comparison of the incidences of the toxemias and eclampsia as they occurred on the entire service and in our particular group is shown in Table VII. One notes that eclampsia is about seven times and the other toxemias about two and one-half times more prevalent in the young group.

TABLE IV. ANTEPARTUM COMPLICATIONS

COMPLICATION	NO. OF CASES	PER CENT
Toxemias	125	19.7
Syphilis	48	7.6
Gonorrhea	14	2.2
Premature separation	7	1.1
Cardiac disease	5	0.8
Condyloma acuminata	5	0.8
Placenta previa	3	0.5
Tuberculosis	2	0.3
Epilepsy	1	0.15
Rickets	1	0.15
Total	211	33.3%

With the toxemia rate as high as it is, there should be little wonder that seven cases of premature separation of the normally implanted placenta were found, provided one accepts the kinship between these two complications.

The rate of maternal syphilis, 7.6 per cent, is lower than the over-all incidence. There was a total of forty-eight patients in this group, forty-three of whom received adequate antisyphilitic treatment, two inadequate, two no treatment, while one was thought to have congenital syphilis.

TABLE V. INCIDENCE OF TOXEMIAS ACCORDING TO AGE GROUP

AGE (YEARS)	NO. OF CASES	NO. TOXEMIAS	INCIDENCE PER CENT
12	3	0	0.0
13	19	8	42.1
14	77	27	35.0
15	163	30	18.4
16	372	60	16.1
Total	634	125	19.7

There were five patients with cardiac disease which we believe is just about the expected incidence for our section of the country. Four were admitted with a history of compensated rheumatic heart disease and all of them were delivered spontaneously without difficulty. We should like to describe briefly the history of the fifth patient.

She was a Negro girl, aged 13 years, who was referred from the cardiac clinic to the obstetrical clinic because of amenorrhea. It was found that she was 12 weeks pregnant. A diagnosis of patent ductus arteriosus had already been made in cardiac clinic. She was then jointly followed by the two clinics. On July 3, 1947, approximately in the twenty-sixth week of gestation, she was operated upon for the cardiac lesion. The postoperative course was most satisfactory. On Oct. 1, 1947, about eight and one-half weeks after the operation, she was delivered spontaneously of a living premature infant weighing 4 pounds and 7 ounces. Six months later, both she and the baby presented themselves for a follow-up visit and were found to be in excellent condition.

Two patients with active pulmonary tuberculosis and one with clinically demonstrable rickets were encountered in the series. Both of these incidences were amazingly low, it was thought, for the type of patients under survey.

The remainder of the complications seem to strike the average and apparently do not require any special comment.

No particular effort was made to classify the type and number of pelvic contractures in this series by clinical measurements. The external mensurations were too incomplete. On admission for delivery, however, where it was indicated, every patient promptly had the relationship between the presenting part and the pelvis estimated and evaluated by x-ray pelvimetry, abdominal palpation, and sterile vaginal examination, if necessary.

TABLE VI. TOXEMIAS, 19.7 PER CENT

TYPE	TERM	PREMATURE	TOTAL	PER CENT
Mild pre-eclampsia	79	13	92	73.6
Severe pre-eclampsia	17	9	26	20.8
Eclampsia	5	2	7	5.6
Total	101	24	125	100.0

The average weight at term for the entire group of these young mothers was 137 pounds. The average net gain for the patients with uncomplicated cases was found to be 23 pounds, whereas that for those with the toxemias was 31 pounds. There were six of them who weighed more than 200 pounds. One was 14 years old, one was 15, and four were 16. The heaviest young primigravida weighed 223 pounds.

TABLE VII. COMPARISON OF INCIDENCE OF TOXEMIAS

	CLINIC	YOUNG
All Toxemias	7.54%	19.71%
Eclampsia	0.61%	1.10%

Labor

Five hundred forty, or 85.2 per cent, of the young mothers in our series were delivered at term, approximately 12 per cent prematurely, and about 3 per cent had previable infants (Table VIII). On this service, babies weighing 3 to 5½ pounds are considered premature and those weighing 1 to 3 pounds previable, in order to comply with the rulings of the Bureau of Statistics of the District. Compared to the statistics of the entire service, in which 87.7 per cent of the deliveries were at term, 9.6 per cent premature, and 2.7 per cent previable, it is observed that the incidence of term deliveries is relatively decreased, whereas that of premature deliveries is increased in the young group.

TABLE VIII. INCIDENCE OF TERM, PREMATURE, AND PREVIABLE DELIVERIES

AGE (YEARS)	NO. OF CASES	TERM	PREMATURE	PREVIABLE
12	3	3	0	0
13	19	16	3	0
14	77	66	11	0
15	163	146	13	4
16	372	309	49	14
Total	634	540	76	18
Incidence	100.0%	85.2%	11.9%	2.9%

The manner in which labor was terminated is revealed in Table IX. Spontaneous delivery was recorded in 68.7 per cent of the cases. Low forceps were required in 23.3 per cent, midforceps in 0.3 per cent, and a Scanzoni rotation in 4.4 per cent of the deliveries, an over-all rate of 28.8 per cent. The application of low forceps was employed twice as frequently in the young mothers, mainly out of consideration of their fright and apprehension and not for obstetrical reasons.

Four of our adolescents had cesarean sections, an incidence of 0.6 per cent. Three of these were performed for cephalopelvic disproportion and one for placenta previa. The rate of this operation is nearly three times greater among the older mothers.

Although one-tenth of the patients in this series had a prolonged labor (thirty hours or more), the average duration of labor for the entire group was thirteen and one-half hours.

The average weight of the term babies was 6 pounds, and 15 ounces, or 3,160 grams. We found among them nine that weighed between 9 and 10 pounds, and two that weighed more than 10 pounds.

TABLE IX. TYPES OF DELIVERY

TYPE	NUMBER	SERIES INCIDENCE	CLINIC INCIDENCE
Spontaneous	438	68.7%	74.7%
Low forceps	148	23.3%	10.8%
Midforceps	2	0.3%	
Scanzoni	28	4.4%	
Breech	16	2.5%	
Version and extraction	1		
Cesarean section	4	0.6%	1.7%

Postpartum Course

The immediate postpartum course of our young mothers was complicated by hemorrhage (500 c.c. or more) on thirteen occasions, a rate of 2.0 per cent, which was slightly higher than that noted for the entire service. Seven of these were attributed to uterine atony, 2 each to premature separation of the placenta and sulcus lacerations, one to a cervical laceration, and one to a retained placenta (Table X).

TABLE X. POSTPARTUM HEMORRHAGE

CAUSES	NO. OF CASES
Atony	7
Premature separation	2
Sulcus laceration	2
Cervical laceration	1
Retained placenta	1
Total	13 or 2.0%
Clinic incidence	1.5%

TABLE XI. PUERPERAL MORBIDITY

TYPE	NO. OF CASES	SERIES INCIDENCE	CLINIC INCIDENCE
Endometritis	22	3.4%	3.5%
Pyelitis	9	1.4%	1.3%
Total	31	4.8%	4.8%
Incidence one-day fever	100 cases or 15.7%		

There were 31 cases of puerperal infection, or a rate of 4.8 per cent (Table XI). Twenty-two, or 3.4 per cent, of these were uterine infections, nine, or 1.4 per cent, were of the upper urinary tract. This incidence corresponds to that of the service. The patients whose puerperium was affected by a one-day fever totaled 100, an incidence of 15.7 per cent. The complications found in this group were divided into the following: endometritis 70, upper urinary tract infections 14, infected episiotomies 5, upper respiratory infections 4, cystitis 3, aspiration pneumonia 1, and unknown 3.

Infantile and Maternal Mortality

Reference to Table XII will indicate that there were 24 fetal deaths, or a total rate of 3.8 per cent, while the entire service's rate was 6.3 per cent. Excluding the 12 previable deaths, the mortality is reduced to 1.8 per cent which is less than half of the service's 4.3 per cent. Of the 24 fetal deaths, 10 were ante partum, 1 intrapartum, and 13 neonatal. Two of the four losses among the term babies resulted from asphyxia associated with prolapsed cord, the third died of an intracranial injury, and the fourth was a neonatal death occurring two days after the infant had been delivered by low forceps of an eclamptic mother. In the premature group of eight infants that did not survive, three of them were born of syphilitic mothers. Two of these mothers had inadequate antisyphilitic treatment and one had none. The remaining five deaths of premature infants were all neonatal deaths. The cause of one of these premature deliveries was eclampsia, of another it was placenta previa, while of three it was not known. Only in one of these neonatal deaths of premature infants was a cause found, aside from the conditions associated solely with prematurity. It was a fractured skull in a baby weighing 3 pounds, 10 ounces, delivered spontaneously.

TABLE XII. INFANTILE MORTALITY, 3.8 PER CENT

	TOTAL DELIVERIES	DEATHS	SERIES INCIDENCE	CLINIC RATE
Term	540	4	0.6%	1.7%
Premature	78	8	1.3%	2.6%
Previable	19	12	1.9%	2.0%
Total	637	24	3.8%	6.3%

There was one maternal death, an incidence of 0.16 per cent or 16 per 10,000 live births. This death was not directly attributable to an obstetric cause. The patient was a registered Negro primigravida, aged 16 years, known to have far-advanced pulmonary tuberculosis. On June 12, 1945, she was delivered spontaneously of a previable infant weighing 2 pounds, 10 ounces. A little over nine weeks after delivery, on Aug. 19, 1945, she died of tuberculosis. An autopsy was not obtained. The total uncorrected maternal mortality rate of the entire series for the same period of time was 0.22 per cent, or 22 per 10,000 live births.

Comment

There are two factors which we believe placed us in an especially advantageous position to undertake this study. The first is the large number of young mothers that came under our observation in a short and recent period of time. The second is that 99 per cent of them were Negroes with little variation in their social and economic status.

The survey has also enabled us to answer with factual data some of the questions that rose in our mind from impressions. It has provoked, furthermore, some thought and speculation on a few points.

From the point of view of frequency, as far as it can be determined, our incidence of 6.3 per cent, or ratio of 1:17, is the highest thus far reported. Fairchild's[2] series which was reported in 1940 totaled 74 young primigravidas collected from 133,361 deliveries occurring in 23 municipal hospitals and one voluntary hospital in and around London. No doubt this incidence in London might have changed now as a result of the war and postwar period. Posner and Pulver's[3] report which was made in 1935 from the Harlem Hospital was based on a study of 100 patients between the ages of 12 and 15 years, inclusive. Since their cases were drawn from a total of 17,000 deliveries, their incidence was 0.58 per cent, or a ratio of 1:170 deliveries. The ratio for the same comparable age group in our series was 1:41.

The mean age for our entire group was 15.4 years. Of particular interest in the age distribution was the fact that two of the three mothers in the 12-year-old group were white and both conceived before menstruation was initiated.

That 85 per cent of them were unmarried is not amazing. It is suspected that any survey of a large number of young primigravidas would disclose the fact that most of them would be unwed.

We are convinced from our observations that the most important consideration to be given the young pregnant girl lies in the management of her antepartum course. There are psychic as well as physical changes that must be borne in mind. The effect of the fear of pain, of reproach, of shame, of the anticipation of an ordeal, and many other mental impacts to which she may be subjected, have to be managed with far more and somewhat different understanding.

The incidence (33.3 per cent) of major maternal complications in our series is higher than Fitzgerald and Grossbard's (20 per cent) quoted in DeLee,[4] and it is considerably higher than the rate of 7 per cent reported by Schmitz and Towne.[1] Pre-eminent among these complications were the toxemias. It was shown that the toxemia rate in our series was 19.7 per cent, or that a toxemia developed in one out of every five young pregnant girls in our group. It was further manifested that among the 211 complications listed, the toxemias produced almost 60 per cent of them, that the younger the patient the higher the frequency of the disease, and finally, that eclampsia occurred seven times and mild and severe pre-eclampsia two and one-half times as frequently in the young group as on the service. The last observation, though it is a little higher in multiples, corresponds to that of Fitzgerald and Grossbard's who found that in their series, eclampsia was five times and the other toxemias twice as prevalent.

What the factors are that produce these striking differences cannot be ascertained, any more than one can tell us yet with finality what causes a toxemia. The circumstances, however, provoke some thought and speculation. Is the high rate—and the younger they are the higher the incidence—among these youngsters the result of the lack of development and balance of their endocrine systems, even though the capacity to conceive is established? Do the stress and strain on their emotions peculiar to their state contribute in any way to these aberrations? Is this incidence so high in our patients because almost all of them are Negroes, for it has been stated that the incidence of hypertension is doubled in the Negro race when compared to the white? These are provocative questions that must be left unanswered by us. On the positive side, we have the inability of a considerable number of these young pregnant girls to appreciate the importance of diet and rest. Besides, we are aware of the disregard that an adolescent can have at times for instructions and restrictions. One of our esteemed colleagues has aptly designated the standard diet selected by these young girls, "the jitterbug diet." It consists of Coca-Cola or Pepsi-Cola, potato chips, salted peanuts, and hot dogs. What a contrast to the salt-free, high-protein diet that is ordered by her obstetrician: The occurrence and frequency of the toxemias in the young primigravida, it seems to us, warrant special exploration and investigation.

When it has been calculated that about 14 per cent of the admissions to the maternity clinic and 12 per cent of the blood bank candidates have positive serological tests, the rate of maternal syphilis, 7.6 per cent, need not be considered high.

The low incidence of tuberculosis and rickets, we believe, is a reflection of the good work that comes from our ably conducted well-baby clinics and health centers.

We found no striking differences in the average weight and the average gain in weight between the mothers in our series and those of the entire service. It was significant, however, that the toxemia patient was 8 pounds heavier at the time of delivery than the patient with an uncomplicated case.

The incidence of premature labor tends to be relatively higher in this group of young mothers. Our rate of nearly 12 per cent approaches that of 11.6 per cent reported by Harris.[5]

The evidence accumulated from this series and others already published uniformly show that obstetrically indicated operative interference for the termination of labor is definitely no higher in the adolescent primigravida. The incidence of cesarean section is decidedly lower. This would seem to indicate that one need not fear the serious problems of cephalopelvic relationship and expect to have more difficult labors and deliveries because the patient is very young and may not yet be considered fully developed.

The average duration of labor, thirteen and one-half hours, in our series conforms to the generally accepted fact that labor is shorter among the adolescent primigravidas.

No appreciable nor compensatory change was noted in the average weight of the baby which in our analysis was 6 pounds and 15 ounces.

The puerperium of the young mothers in our survey was no better nor worse than that observed in the others on our service. The advent of the use of antibiotics and the chemotherapeutic agents prophylactically, as well as therapeutically, has changed and reduced the morbidity of the postpartum course so dramatically, that a new appraisal of the entire question of puerperal infection appears necessary.

From our figures, the chance of obtaining a live baby is decidedly better in the young primigravida. It is evident that one of the most important factors in the improvement of fetal salvage lies in the vigilant and better care that our premature infants are now getting. The cooperation of the pediatrics department in this respect has been a happy and fruitful one.

There was no maternal death directly attributed to an obstetric cause. One patient died of tuberculosis nine weeks after delivery which represents an uncorrected rate of 0.16 per cent or 16 per 10,000 live births. At present, from all the available data at hand, childbirth is safer in the primigravida 16 years old or younger.

Summary

After an analysis of 634 young mothers, 93.7 per cent of whom were primigravidas and 99 per cent were Negroes, we conclude that in our experience the most important phase of their management is found in the antepartum course. The incidence of maternal complications before the baby is born is high and the well-being of the young pregnant girl is especially vitiated by the remarkably high rate of mild and severe pre-eclampsia and eclampsia. The importance of good prenatal care for the young primigravida cannot be overemphasized. Although the ill effects of the toxemias were not appreciably reflected during the course of labor and the puerperium of our patients, their future might well manifest them. Inasmuch as the duration of labor was found shorter, the incidence of cesarean section lower, the complications of the puerperium no greater, and the infantile and materal mortality decreased, we should like to concur with the statement made by Harris[5] that from the purely obstetrical point of view 16 years or less is the optimum age for the birth of the first baby.

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INSENSIBLE AND TOTAL WEIGHT CHANGES DURING LABOR AND DELIVERY AND GYNECOLOGIC OPERATIONS*

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AS A part of our study of the physiology of normal pregnant and pre-eclamptic patients, we wished to know the normal total and insensible weight changes during labor, delivery, and the puerperium, and also during gynecologic operations. These and other studies in water and electrolyte metabolism required a sensitive balance for weighing patients. Because balances of this type are not in stock, and because of the war, a balance was on order since 1943, and one was finally obtained in the fall of 1948. To date, four patients with anuria indirectly owe their lives to daily accurate weights. We found, after our studies were completed, that Wangensteen,[1] since 1947, has been advocating the use of an ordinary weighing scale, which has an accuracy of 100 grams for the weighing of surgical cases, because it is 25 to 50 times more sensitive in the detection of minor changes in body hydration than any other method available.

It has been stated for a long time that the postpartum patient loses weight as a result of delivery, and that the weight loss continues for some days after delivery. The data for several of these observers is given in Table I. Chesley's[2] figures are averages based on some 11,900 cases collected from the literature. Chesley, Stander and Pastore,[3] and Bray[4] report a steady decreasing weight loss for all patients in the early puerperium.

We studied the weight changes of thirty obstetrical patients, twenty-four of whom were delivered vaginally (sixteen primiparas and eight multiparas) and six patients who were delivered by elective cesarean section without labor; and of thirty-one gynecological patients.

TABLE I. AVERAGE LOSS OF WEIGHT AFTER DELIVERY

	AVERAGE WEIGHT GAIN IN PREGNANCY (KG.)	AVERAGE LOSS IN LABOR AND DELIVERY (KG.)	AVERAGE LOSS IN EARLY PUERPERIUM (KG.)	AVERAGE LOSS IN LATE PUERPERIUM (6TH WEEK) (KG.)
Chesley, 1944, collective	10.9	5.45	2.35	
Stander and Pastore, 1940	13.96	5.34	2.30	0.68
Bray, 1938	10.7		2.80	
Our results	11.06	5.818	0.850	0.690

A Sauter beam balance, which is constructed like an analytical balance and has a sensitivity of 0.5 gram, was used to weigh nude patients to within 1 gram (Fig. 1). A wheel stretcher with a detachable top was used for transporting the patient to the scale and weighing.

*This study was supported in part by the Chicago Lying-in Fiftieth Anniversary Research Fund on Eclampsia.

The total weight loss is determined by weighing a patient before and after a given procedure. The insensible weight loss is the difference between the total loss and that attributable to the weight of all ingesta, excreta, blood loss, baby, placenta, and amniotic fluid. The insensible loss, therefore, is the result of water lost in respiration, perspiration, and evaporation from exposed cavities and tissues.

The blood loss was determined by the acid hematin method of Dieckmann and Daily.[5] All the blood-soiled sponges and linens were rinsed at least three times with water, and the resulting solution made up to 4 to 5 liters using $\frac{1}{10}$ normal hydrochloric acid. The milliliters of blood loss were calculated by the formula:

$$\text{Milliliters of blood loss} = \frac{\text{Total grams hemoglobin recovered}}{\text{Grams hemoglobin per cent of patient's blood}} \times 100$$

Our per cent recovery of blood from known controls averaged 93.5 per cent. Two types of control solutions were used. The first consisted of whole blood poured over sponges to which nothing was added except water for rinsing, thus giving a control simulating blood loss as recovered following surgical procedures. Our accuracy was 96 per cent for controls of this type. The second group of controls consisted of whole blood to which were added amniotic fluid, urine, surgical soap, and Merthiolate, thereby employing the contaminants as routinely found in blood recovered from vaginal deliveries. Our per cent blood recovered from controls of this type was 92 per cent.

The obstetrical patients were first weighed immediately following shaving of the vulva and an enema. Throughout labor their intake and output were recorded. All patients with membranes intact after the initial weighing had the membranes artificially ruptured, the fluid collected and measured. The loss of amniotic fluid with the delivery of the baby was measured by collecting all fluid and blood in a pan held beneath the perineum at the time of delivery. The volume of the fluid was measured, the blood volume in the pan calculated and subtracted, the difference in volume being the amniotic fluid. All fluid measurements in milliliters were considered as grams. The fluids were not weighed nor the specific gravities determined. The additional work would not have increased the relative accuracy or value of our results.

TABLE II. AVERAGE TOTAL AND INSENSIBLE WEIGHT LOSS

	AVERAGE TIME		TOTAL WEIGHT LOSS		INSENSIBLE WEIGHT LOSS	
	HRS.	MIN.	KG.	PER CENT	KG.	PER CENT
Vaginal delivery						
Labor	11	20	1.011	1.52	0.608	0.90
Anesthesia and delivery	1	17	4.807	7.51	0.454	0.70
a. Spinal anesthesia and delivery	1	25			0.307	0.48
b. Inhalation anesthesia and delivery	1	9			0.601	0.90
Combined labor and delivery	12	37	5.818	9.03	1.062	1.60
Cesarean section	2	26	6.637	9.2	0.738	1.09
Abdominal hysterectomy	2	7	1.219	2.06	0.759	1.20
Vaginal hysterectomy	2	5	1.370	2.12	0.444	0.70
Vaginal plastics	1	18	1.001	1.31	0.303	0.40
Dilatation and curettage		27	.420	.80	0.233	0.40
Exploratory laparotomy	1	22	.751	.99	0.499	0.60

When each patient had completed the first stage of labor, and it was known that delivery could follow immediately, the patient was weighed for the second time. The short interval of time needed for weighing, with immediate delivery

to follow, was possible largely because spinal anesthesia (saddle block) was used in seventeen of the twenty-four cases. The reason for desiring immediate delivery following the second weighing was to be able to attribute the weight losses in the second and third stages to the anesthesia and operative procedures, and not to additional labor on the part of the patient.

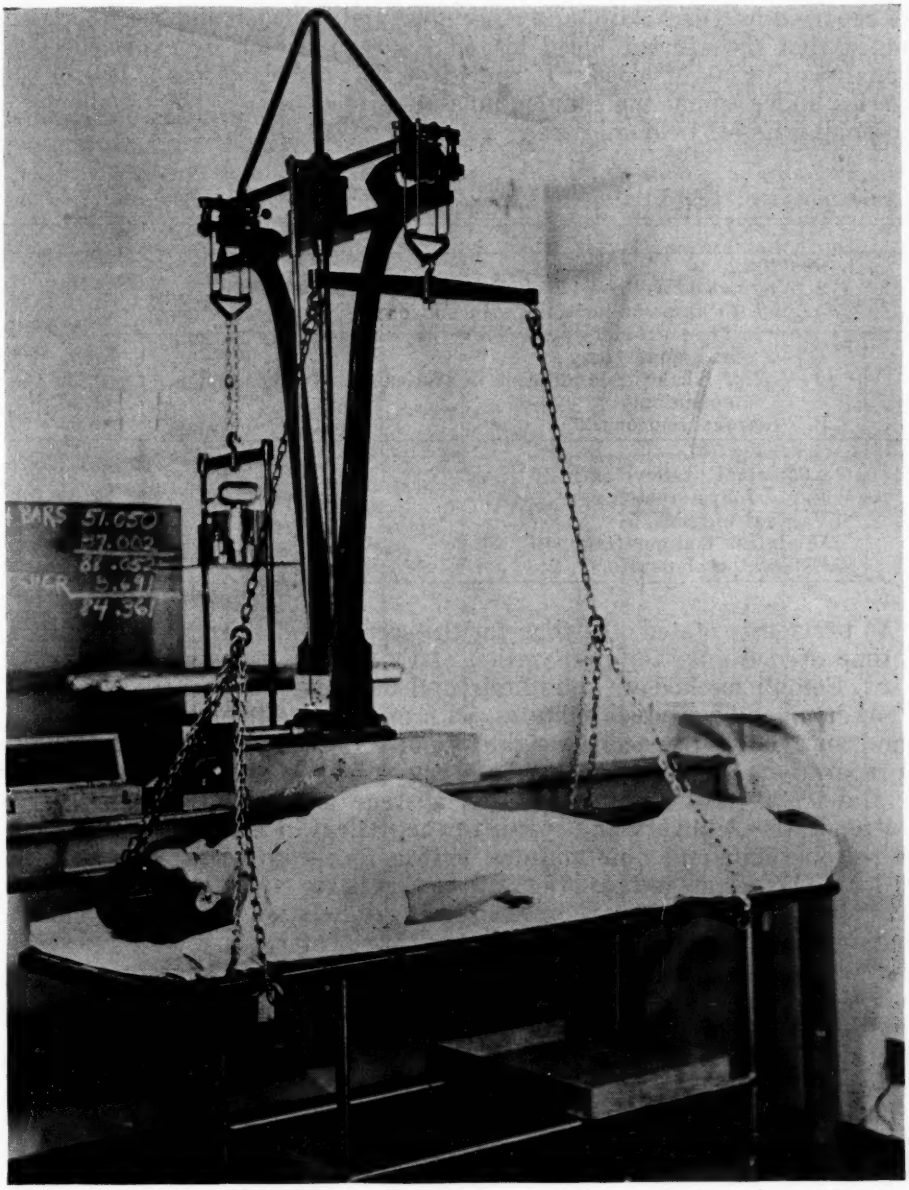

Fig. 1.—Sauter balance. The beam rests on a 5 by 8 inch I beam which is rigidly bolted to 3½ inch pipe anchored to the floor. A set of metric weights and weighed iron window counter balances and lead pigs are used.

Our data concerning the total and insensible weight loss relative to delivery or a gynecologic procedure are given in Table II. The average length of observation in labor was eleven hours and twenty minutes. The average fluid intake during this period of labor was 560 ml., and the average urinary output was

280 ml. The average total weight loss per patient was 1.011 kg., with an average insensible weight loss of 0.608 kg., representing 0.90 per cent of the total body weight.

The average blood losses for the obstetric and gynecologic cases are listed in Table III. The blood loss for various obstetrical procedures are similar to those reported by Dieckmann and associates[6] and by Odell and Seski.[7] It should be noted that the average blood loss at cesarean section by experienced obstetricians was 618 ml. of blood. It is evident that the blood loss is less in vaginal deliveries under spinal than under inhalation anesthesia. The number of cases is too small for statistical analysis.

TABLE III. TYPE OF OPERATION AND BLOOD LOSS

	AVERAGE (ML.)
I. *Obstetrical.*—	
A. Vaginal deliveries 24 including 1 spontaneous delivery and 2 Dührssens incisions with midforceps	331
1. 14 spinal anesthesia deliveries with low forceps and episiotomy	278
2. 7 inhalation anesthesia deliveries with forceps and episiotomy	325
B. Cesarean sections, 6	618
II. *Gynecological.*—	
Abdominal hysterectomy, 10	167.5
Vaginal hysterectomy, 4	743.0
Vaginal plastics, 5	380.0
Dilatation and curettage, 10	65.0
Exploratory laparotomy, 2	51.0

As previously stated, the time for the second and third stages of labor was that time needed only for preparation of the patient, anesthesia, delivery, and repair. For all methods of anesthesia and delivery, the average time required was one hour and seventeen minutes, with an average total weight loss of 4.807 kg. and an average insensible weight loss of 0.454 kg. The average time taken for preparation, delivery, and repair of the spinal-anesthetized patient was one hour and twenty-five minutes, with an average insensible weight loss of 0.307 kg. Preparation, delivery and repair of the patient, using inhalation anesthesia, averaged one hour and nine minutes, with a resulting insensible weight loss of 0.601 kg. This would indicate that, all factors being equal, the insensible weight loss is twice greater with the patient using inhalation anesthesia than under spinal anesthesia (Table II).

It was necessary to weigh accurately each baby and placenta in order to calculate insensible weight loss. It is interesting to note that the average weight of the babies of the vaginal group was 3.247 kg. and the average weight of the placenta was 0.532 kg., in contrast to the average weight of the cesarean babies which was 3.408 kg. with an average placental weight of 0.634 kg.

Each cesarean-section patient was weighed immediately before and after operation. Spinal anesthesia was used in every case. The average time interval between weighings was two hours and twenty-six minutes. The average blood loss was 618 ml. The average total weight loss was 6.637 kg. and the average insensible weight loss was 0.738 kg. (Tables II and III).

All postpartum patients in both the vaginal and cesarean groups were weighed on their 4th, 7th, 10th, and 42nd postpartum days. The weight changes are based on a gain or loss in the interval between weighings; for example, between the immediate postpartum and the 4th day, between the 4th and 7th days, etc. Our results demonstrate that not all patients show a progressive decrease in weight during the first ten days of the puerperium. We found that

63 per cent of the vaginal-delivery patients showed a gain on the fourth postpartum day over their immediate postpartum weight, 8 per cent on the seventh day, and 4 per cent on the tenth day (Table IV).

The cesarean-section group also showed that there was not a steady, progressive weight loss post partum, but that 33 per cent showed a gain on the fourth day over their immediate postpartum weight, 17 per cent on the seventh, but no weight gain on the tenth postoperative day (Table IV).

These results differ markedly from those obtained by Chesley, Stander and Pastore, and Bray, whose results show a steady, decreasing weight loss for all patients in the early puerperium, the average weigh loss equalling about 2.5 kg. The recent work of Romero,[8] who weighed patients the morning after delivery and again on the fifth and sixth days post partum, showed that 64 per cent of his patients showed a postpartum weight gain from 1 to 1,100 grams, and that only 36 per cent showed a weight loss.

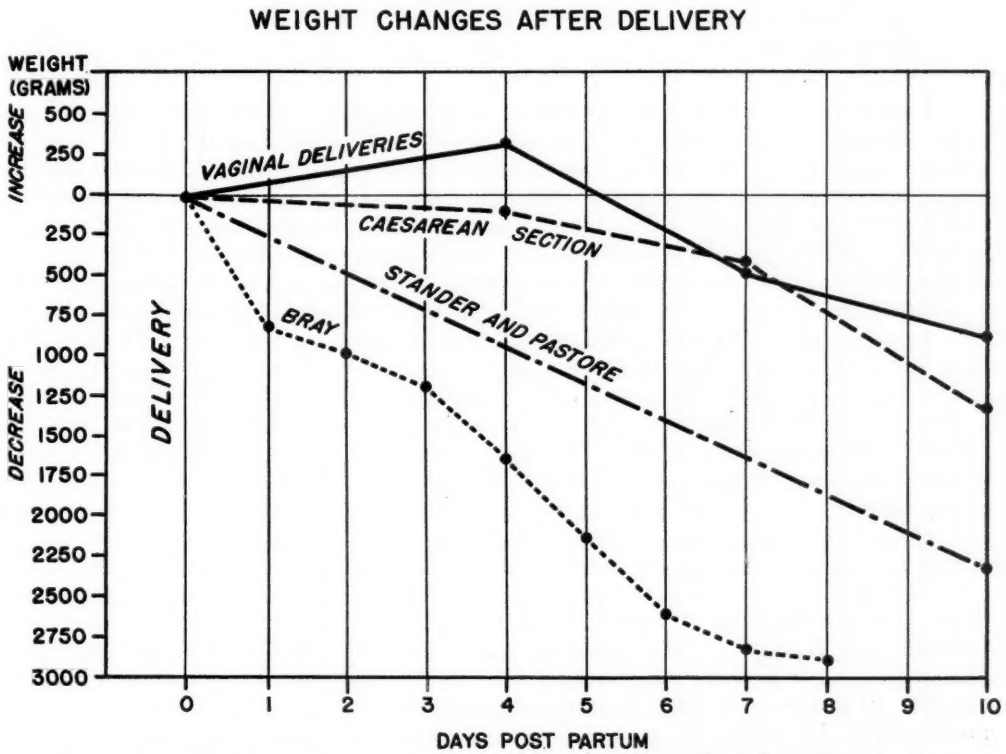

Fig. 2.—Curves illustrating changes in body weight beginning immediately after delivery and continuing up to the tenth postpartum day.

Our findings, along with those of Romero, differ from these earlier reports in that: (1) Patients in our series averaged less total weight loss in the early puerperium (0.850 kg.). (2) All patients did not show a steady loss throughout the puerperium. As many as 63 per cent showed a gain over their immediate postpartum weight to the fourth day. The earlier reports were based on work done largely prior to 1940. Bray, in 1938, used a similar weighing procedure to ours, and has graphed his findings using the means of all cases. Our findings are plotted with those of Bray and Stander in Fig. 2.

The difference is probably due to the early ambulation and early return of both obstetric and gynecologic patients to a normal diet; the former within twenty-four hours after delivery, and the latter within seventy-two hours. The

amount of vomiting, both in obstetric and gynecologic patients, with improved anesthesia is much less than formerly. After spinal anesthesia it is rare.

The forty-second day weight changes in our series were nearly equal to those obtained by Stander showing an average weight loss of 0.690 kg. Thirty-three per cent of these patients had gained over their hospital discharge weight.

TABLE IV. CHANGES IN WEIGHT DURING THE PUERPERIUM

		POSTPARTUM DAYS			
		4TH	7TH	10TH	42ND
Weight Changes Based on Per Cent.—					
Vaginal delivery	Gain	63	8	4	32
	Loss	37	92	96	68
Cesarean section	Gain	33	17	0	33
	Loss	67	83	100	67
Average Weight Changes Per Patient in Kilograms.—					
Vaginal delivery		+.321	−.436	−.850	−.690
Cesarean section		−.015	−.301	−1.365	−.882

Thirty-one gynecological patients were weighed immediately before and after surgery. The intake and output were recorded during the operative procedure, weight of the specimen determined immediately upon removal and the blood loss calculated by the method previously described. The average blood loss is given in Table III. The blood loss of 167 ml. for abdominal hysterectomies is small. With vaginal hysterectomies, the 743 ml. of blood loss is due, in part, to the anterior and posterior plastic operation which is also carried out. This is substantiated by the blood loss of 380 ml. found with vaginal plastics alone. The average total and insensible weight loss is given in Table II. It is evident that the total weight loss is greater after vaginal hysterectomy than any other gynecologic procedure because of the blood loss. However, the insensible loss is greatest after abdominal hysterectomy because of the evaporation from the viscera. This has been known for many years, but very few surgeons attempt to prevent evaporation at the time of laparotomy. Vaginal hysterectomy without plastic repair would have much less blood loss, and the insensible weight loss would be decreased. Thus, it is evident why simple vaginal hysterectomy causes less disturbance in the patient, especially if she is not a good operative risk.

The gynecologic patients were again weighed on their tenth postoperative days, and the changes in weight from their immediate postoperative weight are recorded in Table V. The patients who had a dilatation and curettage were discharged on the third or fourth day. Fifty per cent of the abdominal and vaginal hysterectomy and exploratory laparotomy patients gained in weight postoperatively, while 50 per cent lost in weight. One of the vaginal plastic patients gained, while three lost in weight.

TABLE V. CHANGES IN WEIGHT ON THE TENTH POSTOPERATIVE DAY

	ABDOMINAL HYSTERECTOMY	VAGINAL HYSTERECTOMY	VAGINAL PLASTIC	EXPLORATORY LAPAROTOMY
Gain per cent	50	50	25	50
Loss per cent	50	50	75	50

Comment

Sullivan[9] weighed 151 patients after surgery of the stomach, colon, and rectum, and recorded gains or losses on the basis of 2.5 per cent of the total body weight. His data are compared with ours in Table VI. Over 75 per cent of his patients had a weight loss greater than 2.5 per cent of the body weight.

Only 15 per cent of our gynecologic patients had a postoperative weight loss greater than 2.5 per cent of the body weight. Adolph and co-workers[10] have shown that a 2 per cent decrease in body weight due to dehydration can be detected by symptoms and signs and with each additional water deficit the changes in the body and the symptoms and signs become more serious. It is readily understandable then why patients who are not good surgical risks as a result of dehydration from various causes, from malnutrition or anemia, as well as patients who are good risks but who lose excessive amounts of blood or in whom the abdominal cavity is open for an undue length of time, are likely to go into shock. It is also obvious why such patients may have an oliguria or an anuria postoperatively, and unless properly treated develop uremia and die. Wangensteen thinks that the weight fluctuation should not exceed 2 per cent of the body weight.

TABLE VI. POSTOPERATIVE WEIGHT CHANGES OF SURGICAL PATIENTS

	GAINED OVER 2.5%	STAYED WITHIN 2.5%	LOST OVER 2.5%
Sullivan	7.3%	11.2%	76.8%
Our results	11.2%	75%	14.8%

The insensible weight loss for labor and delivery is 1.062 kg. occurring in an average of twelve hours. For the same time, the average intake is 560 ml. and the urine 280 ml. In protracted labor, the insensible weight loss obviously can become quite great, and is an important contributory factor to the shock which so frequently follows delivery in these patients with reported minimal blood loss. Our experience has been that the accurately measured blood loss is two to four times the estimate. Furthermore, Dieckmann[11] has shown that there is a hemoconcentration in normal labor which, of course, would be much greater in prolonged labor. Thus the blood lost at delivery contains a greater concentration of hemoglobin. In the present study, we determined the hematocrit values in early labor, within twelve hours post partum, and on the fourth partum day. The mean values were 37.4, 39.5, and 36.5 volumes per cent. None of our patients showed significant clinical findings of dehydration. However, all of us have seen the dry lips, increase in temperature, etc., found in neglected patients who have had abnormally long labors.

The insensible weight loss is shown to be twice as great when using inhalation anesthesia for vaginal deliveries as when using spinal anesthesia. Similar comparisons can be shown with gynecological cases. Inhalation anesthesia was used for each case of dilatation and curettage, with a calculated insensible weight loss of 0.233 kg., as compared with an insensible weight loss of 0.274 kg. in vaginal plastic cases where spinal anesthesia was used. This slight difference in insensible loss of the two groups becomes significant when it is noted that the average length of time of the spinal anesthesia was three times that of the inhalation.

We have found that the insensible weight loss is more than twice as great with a laparotomy than in procedures that are extraperitoneal, time and type of anesthesia being equal.

Evaporation from the abdominal cavity is rapid and is an important factor in the insensible weight loss of some 0.759 kg. in a gynecological operation and 0.738 kg. in a cesarean section.

No special measures at present, other than the patient's desire to drink, should be used to maintain the water balance during a normal labor of ten to twenty-four hours. In longer labors, 5 per cent glucose or saline solution should

be injected parenterally at the rate of 1,000 to 2,000 ml. per twenty-four hours. The hemoglobin or hematocrit concentration or the weight of the patient should be the guide. The urine output is not of much value.

We are not certain that the parturient patient should be kept in water balance. Other data seem to indicate that a slight degree of maternal dehydration is best for the fetus.

Conclusion

Periodic weights of patients, whose labor is over twenty-four hours or who are seriously sick after operation, are of much more value than attempts to correlate intake and output. A beam balance is desirable for research purposes but an ordinary carefully adjusted scale will suffice for clinical care of patients.

Blood loss is always one to four times greater than the estimated amount.

There is a negative water balance of approximately 1 kg. during labor, of which 0.6 kg. is insensible weight. There is an additional insensible loss during delivery of 0.3 to 0.6 kg., depending upon the anesthetic used. Spinal anesthesia has the lower loss.

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GELFOAM, VAGINAL SMEAR, AND BIOPSY IN THE DIAGNOSIS OF UTERINE CARCINOMA

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THE vaginal smear in the diagnosis of uterine carcinoma as developed by Papanicolaou and Traut[1, 2] is now used extensively. Less widely known and used is the Gelfoam sponge biopsy method introduced by Gladstone.[3, 4] Both methods are made possible by the exfoliation of individual cells and sheets of cells from normal and pathological epithelial surfaces. The possibility of frequent repetition without trauma and their simplicity are distinct advantages of these methods.

As stressed by Foote and Li,[6] it is desirable to evaluate any method that may be of aid in the detection of cancer in its early stages. The vaginal smear is known to be accurate and reliable but is time consuming. Foote and Li, using an incidence of one in fifteen hundred women over the age of 35, determined that it would require five hundred hours of microscopy to detect one carcinoma of the cervix in the general population of women 35 years of age and over. This cost in time expenditure occasions resistance to the vaginal smear method and any method which limits the search in time and space is worthy of trial. The purpose of this investigation was to test the Gelfoam method, compare it with the Papanicolaou smear, and to present our findings in a series of suspicious cases followed on the Gynecological Service at Queens General Hospital in which biopsy, vaginal smear, and Gelfoam methods were used.

Material Studied and Methods

Beginning Feb. 1, 1949, vaginal smear and Gelfoam biopsy were taken, in conjunction with formal biopsy, in sixty-eight cases suspicious for carcinoma. This was not a routine survey, for only those cases presenting signs and symptoms of possible malignancy were chosen for investigation in this manner.

The smears were taken from the vaginal pool and by wiping across the suspected region. No special instruments or forceps were used, a single cotton applicator being employed to transfer the specimen to a glass slide. A thin smear was immediately made and fixed and later stained by the Papanicolaou technique. Smears in approximately 10 per cent of the cases were repeated for poor staining or negative results when positive results were expected. The criteria used in selecting malignant cells in the Papanicolaou smears were those described in the monograph by Papanicolaou and Traut.[2] Opinions on the Papanicolaou smears were expressed in accordance with his classification.

The sponge used was Gelfoam No. 12 (Upjohn), cut into centimeter squares. The cervix was gently wiped with ordinary gauze and the Gelfoam placed firmly against it for thirty seconds and then rubbed briskly across the

surface. It was then placed in 10 per cent formalin. The early specimens were embedded without identification of the side placed against the cervix. Later, the side placed against the cervix and to be cut by the microtome was identified by markings with Zephiran. Still later this was obviated by use of both sides of the Gelfoam square.

The Gelfoam was not treated selectively and examination corresponded to the routine surgical material, the slides being at first studied in the usual rapid routine of a busy surgical pathological service, very often for a few seconds and in no instance for more than one or two minutes.

The initial Gelfoam results were based on data obtained by the above methods. Opinions were expressed as positive or negative with no allowance for suspicious cases at the beginning. At a later date the Gelfoam slides were again reviewed and classified positive, negative, or suspicious. Finally, recuts were done on blocks of those initially reported negative and such recuts were carefully studied with interesting observations recorded separately below.

Results

Table I presents the results in all cases positive for uterine malignancy. Of the suspected sixty-eight cases, seventeen were positive. Included is one case of carcinoma of the vulva, one of primary adenocarcinoma of the tube, and two cases of adenocarcinoma of the fundus. All of the Papanicolaou smears agreed with biopsy or surgical findings in these seventeen cases, except for the one case of tubal adenocarcinoma, the surgical specimen of which showed that positive smear could not reasonably be expected. Two vaginal smears were classified suspicious, Class III. One of these was from a smear taken in pregnancy with a suspicious cervical erosion, the other was from a smear taken in a case of chronic cervicitis with hyperplastic changes. Three vaginal smears were classified positive, Class IV and were in error. These results are shown in Table II.

TABLE I

	IDENTIFICATION		PAPANICOLAOU SMEAR*	GELFOAM FINDINGS†	BIOPSY DIAGNOSIS
1.	D. K.	1-49-98, 2-49-104	V	+	Squamous carcinoma, Grade 2
2.	Q. L.	2-49-163	V	+	Squamous carcinoma
3.	E. L.	3-49-95	V	+	Squamous carcinoma, Grade 2-3
4.	A. B.	3-49-18	V	+	Squamous carcinoma, Grade 3
5.	H. P.	3-49-94	V	+	Squamous carcinoma, Grade 2
6.	E. H.	2-49-187	V	±	Squamous carcinoma, Grade 2
7.	E. A.	3-49-235	V	+	Squamous carcinoma, Grade 2
8.	S. B.	3-49-276	V	+	Squamous carcinoma, Grade 3
9.	M. B.	4-49-90, 4-49-140	V	+	Adenocarcinoma, fundus, mucogenic secreting features
10.	M. B.	4-49-139, 4-49-14	V	–	Adenocarcinoma, fundus
11.	R. C.	4-49-116	V	–	Squamous carcinoma
12.	A. I.	4-49-147	V	+	Squamous carcinoma, Grade 4
13.	A. P.	4-49-201	V	+	Squamous carcinoma
14.	F. B.	4-49-226	IV	+	Squamous carcinoma, vulva
15.	C. W.	5-49-54	V	+	Squamous carcinoma, Grade 3
16.	M. B.	5-49-135	V	+	Squamous carcinoma
17.	E. P.	5-49-62, 5-49-147	I	–	Adenocarcinoma, tube

*Class I, absence of abnormal or atypical cells.
Class II, atypical cells present but without abnormal features.
Class III, cells with abnormal features but not sufficiently pathognomonic.
Class IV, fair number of pathognomonic cells and cell clusters.
Class V, large number of conclusive cells and cell clusters.
†Positive, +
Negative, –
Suspicious, ±

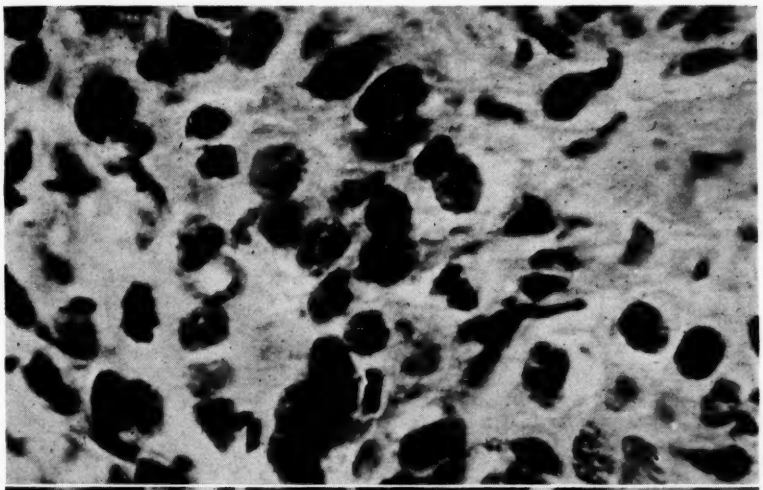

Fig. 1.

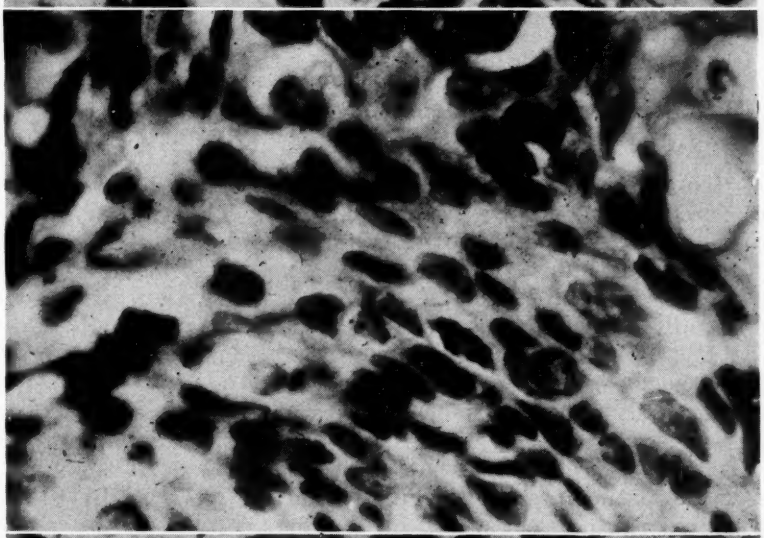

Fig. 2.

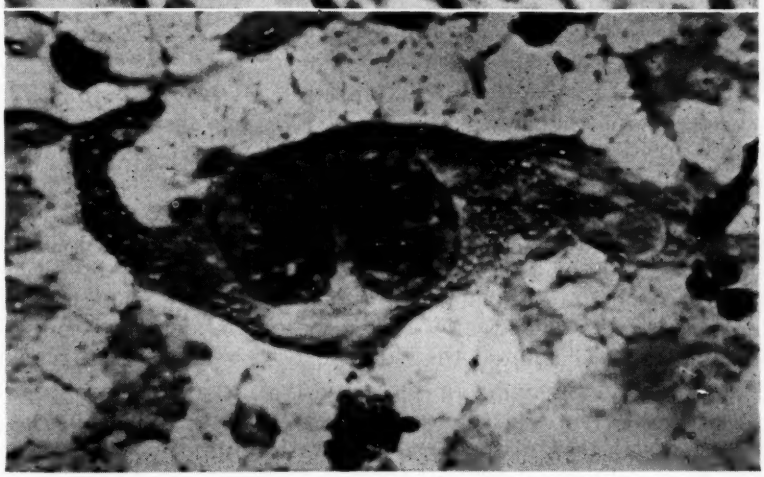

Fig. 3.

Fig. 1.—Biopsy of the cervix, Case 3. Squamous-cell carcinoma, grade 2.
Fig. 2.—Gelfoam biopsy, Case 3. Gelfoam has picked up a large group of malignant cells.
Fig. 3.—Papanicolaou smear, Case 3. Shows typical cellular changes found in pathognomonic cells.

TABLE II

	IDENTIFICATION		PAPANICOLAOU SMEAR	GELFOAM FINDINGS	BIOPSY DIAGNOSIS
18.	E. S.	2-49-247	IV	–	Chronic cervicitis, squamous metaplasia, intraepithelial cells with atypical cytology
19.	R. S.	3-49-62, 4-49-173	IV	–	Chronic cervicitis, multiple small polyps
20.	M. B.	3-49-24, 3-49-44	III	–	Chronic cervicitis, hyperplastic changes
21.	M. R.	4-49-18, 3-49-142	IV	–	Chronic cervicitis, squamous metaplasia
22.	A. S.	3-49-180	III	–	Chronic cervicitis

In all sixty-eight cases no Gelfoam was classified falsely positive. Six Gelfoam specimens were classified negative and one as suspicious in cases proved to be positive for uterine carcinoma. Recut specimens of these are discussed below.

In the remaining forty-six cases, all negative for carcinoma, the smear, Gelfoam, and biopsy agreed and were negative throughout.

Comment on Results

Recut Gelfoam specimens (two additional sections from the same block) were taken from six cases initially classified as negative (Cases 2, 6, 10, 11, 14, 16) and one case initially classified as suspicious (Case 9). These seven cases were found to be positive by formal biopsy. The recut of the Gelfoam in Case 2 showed one clump of cells definitely suggestive of carcinoma. In Case 6 there were very definitely suspicious cells in the recut and review of the original slide now revealed one small clump of suspicious cells which, though small, were atypical and should properly have been called positive. Recut of Gelfoam in Case 9 showed malignant cells but the type of carcinoma could not be determined. Recut of Gelfoam preparations in Cases 10 and 11 remained falsely negative. The latter showed so much blood that tumor cells may have been obscured. Recut of Gelfoam in Case 14 showed low-grade squamous-cell carcinoma, pearls being found (Fig. 8). Recut of Case 16 showed definite malignant cells.

Figs. 1 to 3 present the findings in a case in which biopsy, Gelfoam, and smear all were positive. Figs. 4 and 5, Case 10, show adenocarcinoma of the fundus in which the Gelfoam failed. Three of the four vaginal smears taken in this case were also negative. The fourth smear was very definitely positive as can be seen in Fig. 4. This was a well-differentiated glandular tumor, Fig. 5. Infrequent desquamation perhaps accounts for the negative smears.

Cases 18, 19, and 21 illustarate the warning often repeated by Papanicolaou,[5] i.e., smear should not be specified positive unless the evidence is overwhelming. Case 21 is of further interest in that the biopsy, Fig. 6, showing chronic cervicitis with metaplasia, also reveals the same process in the vaginal smear, Fig. 7. It was these cells which were mistaken for malignant cytological elements and occasioned the false-positive reading in this instance.

The Papanicolaou smear has a distinct advantage in permitting meticulous cytological studies. The Gelfoam has a disadvantage of giving less detail in the nuclear structure in routine formalin fixation and hematoxylin-eosin staining. There is a compensating advantage, however, in that the entire slide need not be explored. The cell groups in question are found on the surface or superficially embedded in the Gelfoam and the appearance of the cells corresponds to the ordinary tissue preparations to which pathologists are ac-

customed without additional special training. The timesaving feature of the Gelfoam procedure may bring the routine survey of unsuspected cases in cancer detection clinics into the practical realm.

Fig. 4.

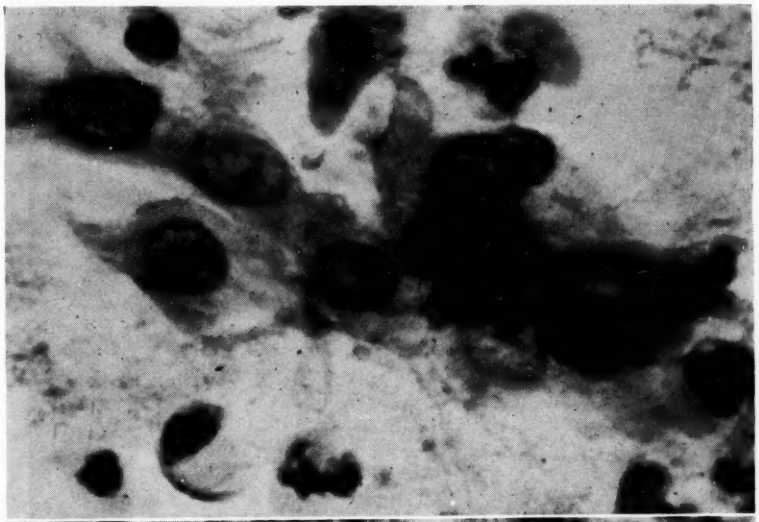

Fig. 5.

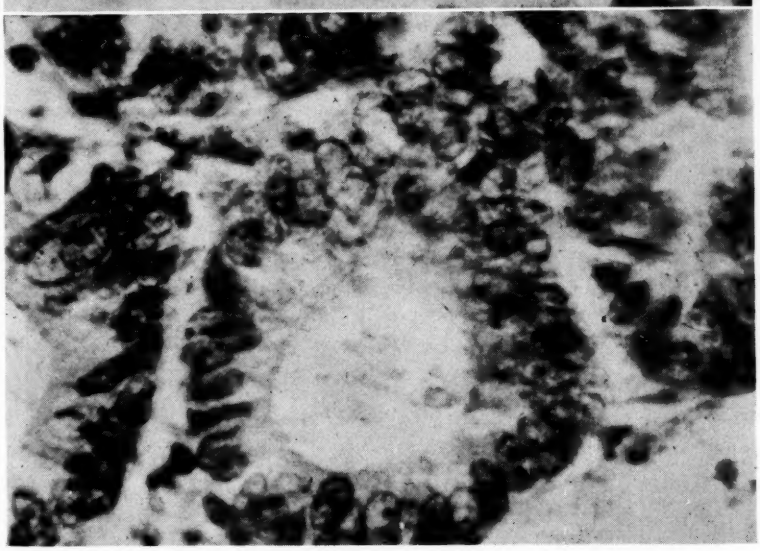

Fig. 4.—Papanicolaou smear, Case 10. Positive smear in case of adenocarcinoma of the fundus. Gelfoam failed to reveal the pathology in this case.

Fig. 5.—Biopsy (curettage). Same case as in Fig. 4, showing well-differentiated glandular tumor. Three of four smears in this case were negative, the fourth was definitely positive as can be seen in Fig. 4.

It occurred to one of the authors that the use of the cotton swab for the preparation of vaginal smears undoubtedly leads to loss of valuable material which is discarded in the saturated cotton after the smears are made. It was found that the Gelfoam was of ideal consistency and adsorbent properties to be used in place of the absorbent cotton. This would permit the use of the Gelfoam for *both* preparations, that is, the Papanicolaou smear and the Gelfoam biopsy.

The use of both procedures can be made complementary and particularly so in suspicious cases. This applies for adenocarcinoma of the fundus where exfoliation may vary and cannot be produced directly by the physician under direct observation. Both procedures require confirmation by the formal biopsy where focal lesions are available.

Fig. 6.

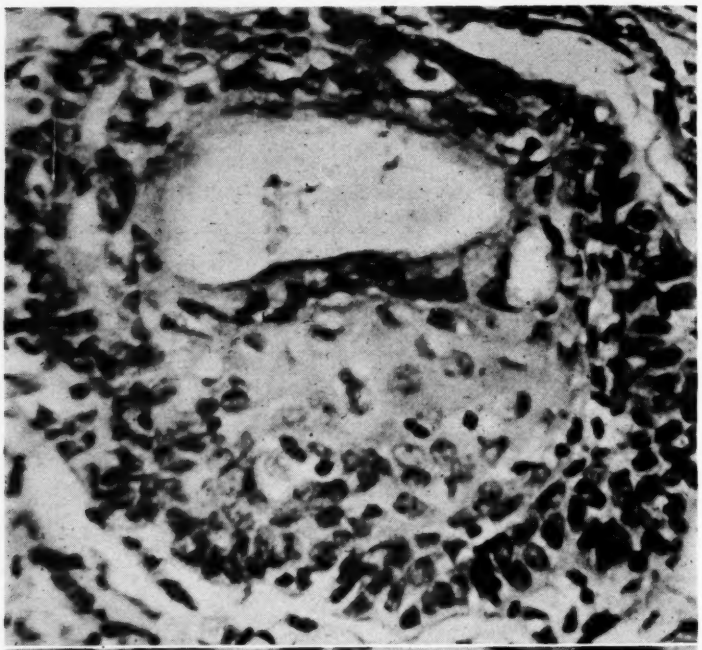

Fig. 7.

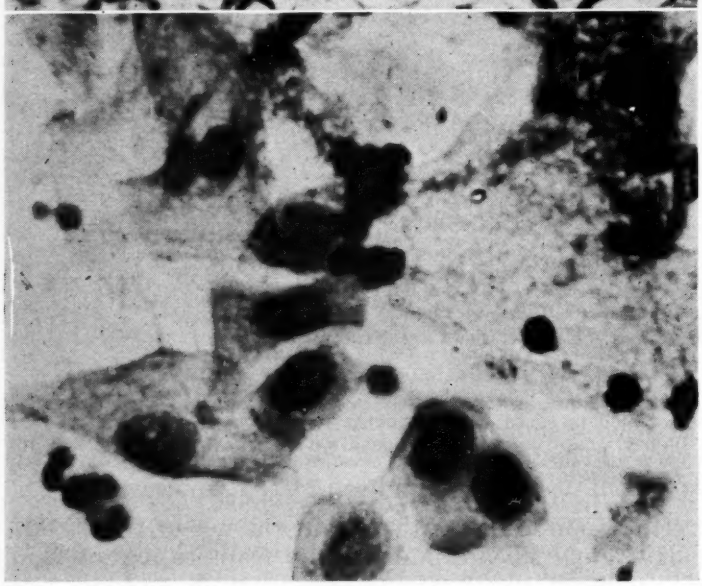

Fig. 6.—Biopsy of the cervix, Case 21. Chronic cervicitis with metaplasia. Columnar cells are being pushed toward the center of the gland lumen by squamous cells beneath.

Fig. 7.—Papanicolaou smear, same case as Fig. 6, showing the same process as seen in the biopsy. These cells were mistaken for malignant cytological elements.

It is wrong to have the formal biopsy replaced by such procedures. Occasionally the exfoliative studies will be positive and no focal lesion for biopsy will be detectable. Under such circumstances and when the initial biopsy is negative, the authors believe that a knife conization of the cervix should be done and the specimen sent to the laboratory with request for complete survey by multiple blocks.

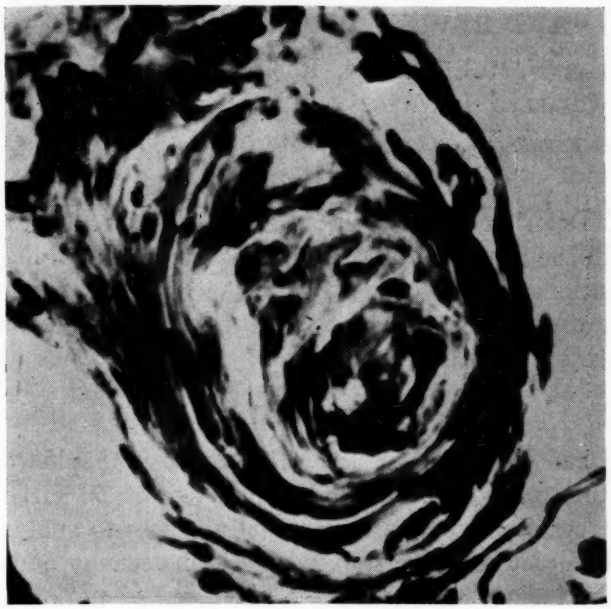

Fig. 8.—Gelfoam biopsy. Recut of Gelfoam, Case 14, showing pearl formation in low-grade squamous-cell carcinoma.

Summary

1. The results of a comparison of the formal biopsy and exfoliative cytological studies, by means of the Papanicolaou smear technique and the Gladstone Gelfoam procedure, are presented in sixty-eight cases of suspected uterine malignancy.

2. The Papanicolaou smear technique and the Gelfoam biopsy method are found to be worthy adjuncts in the diagnosis of carcinoma of the cervix.

3. The Gelfoam biopsy procedure is superior from the standpoint of time saving and can readily approach the accuracy of the vaginal smear.

4. A procedure is recommended which permits the vaginal smear and the Gelfoam biopsy to be combined in a single study.

The authors wish to acknowledge the aid of Dr. Samuel A. Goldberg and Miss P. Stanley of the New Jersey State Department of Health in the preparation of the microphotographs shown in this study.

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SPLENECTOMY DURING PREGNANCY, WITH A REPORT OF 5 CASES AND REVIEW OF THE LITERATURE

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BARNES and Doan[3] recently reported three cases in which splenectomy was performed in the course of pregnancy because of critical hematologic indications. They mentioned that no similar series had come to their attention. They observed further that splenectomy for blood dyscrasias complicating pregnancy had been previously reported only ten times.

Material

We recently had occasion to review all of the cases of splenectomy performed at the Mayo Clinic on women of childbearing age or on girls who have since reached the childbearing age. Our principal aim was to analyze the gestations that may have occurred in these women since splenectomy and to formulate, if possible, some conclusions concerning the likelihood of normal pregnancy after splenectomy. This study was a continuation, so to speak, of an earlier presentation of Mussey and Burkley.[22] As a result of our review of the records, we discovered five cases in which splenectomy was performed in the course of pregnancy. We plan to report these five cases briefly and to present in tabular fashion all of the cases of splenectomy in the course of pregnancy that have come to our attention in the literature. We are well aware that cases exist which have not been reported and, in addition, that we may have overlooked certain published information despite our efforts to make our data complete.

Report of Cases

CASE 1.—A woman, 24 years old, underwent splenectomy in November, 1917, for congenital hemolytic icterus. On admission to the clinic she had complained of weakness and easy fatigability and had reported a positive family history for this disease, in that one brother had hemolytic jaundice. The patient was in the fourth month of her first pregnancy at this time. Laboratory study revealed that the concentration of hemoglobin was 45 per cent of normal, the erythrocyte count was 1,990,000 per cubic millimeter of blood and increased fragility of the erythrocytes was present. On physical examination, the spleen was enlarged to the iliac crest. Splenectomy was performed and the convalescence was uneventful. The patient was dismissed from the hospital on the twelfth postoperative day. She was delivered of a normal infant elsewhere, at term, after a difficult labor that was terminated by the application of forceps. This patient subsequently had three uncomplicated pregnancies.

CASE 2.—A multipara, 34 years old, registered at the clinic in 1927. Her chief complaint was of an abdominal tumor that had been present for three years. The patient was in the third month of a pregnancy at the time of admission. The spleen was enlarged, grade

3 (on a grading basis of 1 to 4, in which 1 is the least and 4 the most) and the liver was also palpable. The concentration of hemoglobin was 68 per cent of the normal, the leucocyte count was 10,300, the coagulation time 6 minutes, the bleeding time 2 minutes, the platelet count 230,000, and the fragility of the erythrocytes was normal. The tentative diagnosis was either infectious splenomegaly or splenic anemia. A spleen which weighed 986 grams was removed by Dr. C. H. Mayo and the patient's recovery from the operation was uneventful. Delivery occurred at term elsewhere and the infant was normal. On the fifteenth postpartum day, the patient suffered a "stroke" and died twelve hours later. She had had severe pain in the right lower portion of the thorax from the second day of her confinement.

CASE 3.—A pregnant woman, 27 years old, who had borne one child, registered at the clinic in August, 1932. Her chief complaints were of jaundice and weakness. Her father and a sister had a history of jaundice. Three years before admission, in her first pregnancy, the patient had had eclampsia. Five months before admission, she had become pregnant.

On examination at the clinic the spleen was palpable to the umbilicus and the liver was also enlarged. Laboratory study revealed 10.2 Gm. hemoglobin per 100 c.c. of blood, the leucocyte count was 11,900, the blood smear was said to be typical of congenital hemolytic icterus, and the fragility of the erythrocytes was increased. A diagnosis of congenital hemolytic icterus was made.

Splenectomy was performed and the postoperative course was without incident. The spleen weighed 1,000 grams.

The patient received the rest of her prenatal care elsewhere and was delivered when she was three to four weeks past the expected date of confinement. An instrumental delivery was performed and a female child was born that lived about thirty minutes. The patient subsequently wrote that she had been extremely ill at the time of her delivery and had been "practically blind" during birth and for several days thereafter.

CASE 4.—A woman, 37 years old, registered at the clinic in December, 1942. Her chief complaint was jaundice and on questioning it was found that other members of her family had had hemolytic icterus. She was in the third month of her third pregnancy at the time of admission.

On examination, the spleen was found to be enlarged and to extend to the level of the iliac crest, the value for hemoglobin was 7.8 Gm. per 100 c.c., the erythrocyte count was 2,860,000, the leucocyte count was 8,600, and the reticulocyte count was 7.8 per cent. The spleen, which weighed 997 grams, was removed without incident. Convalescence was uneventful. The patient was delivered of a stillborn infant elsewhere after six and one-half months of pregnancy.

CASE 5.—In October, 1942, a married woman, 22 years old, presented herself in the thirty-sixth week of her first pregnancy. She stated that for the preceding six days purpuric spots had been noted on the lower extremities and abdomen and she had experienced bleeding from the gums. Her physician had discovered a marked reduction in the number of platelets and increased bleeding and clotting times. Transfusions were employed on five occasions.

Laboratory studies on admission revealed 16.6 Gm. hemoglobin per 100 c.c., 4,880,000 erythrocytes, 14,000 platelets, a bleeding time of 10 minutes, and a clotting time of 11 minutes. A diagnosis of idiopathic thrombocytopenic purpura was made. There was no clot retraction at the end of nine hours. There was some debate as to whether or not an immediate splenectomy should be performed but on October 9, five days after admission, splenectomy was done. At operation the spleen was found to be about twice normal size, some adhesions were freed with difficulty, and no accessory spleen was found. The spleen weighed 290 grams. Seven days later, spontaneous labor of eight hours' duration occurred. A left mediolateral episiotomy, grade 2, was done and an outlet forceps delivery was conducted. Hemorrhage consisting of about 350 c.c. of blood occurred. The platelet count of the child was 88,000 at time of delivery and the bleeding time was 2½ minutes. The male infant

TABLE I. CASES REPORTED IN THE LITERATURE

CASE	AUTHOR AND YEAR OF PUBLICATION	AGE IN YEARS	GRAVIDA; PARA	INDICATION FOR SPLENECTOMY	MONTH OF PREGNANCY IN WHICH SPLENECTOMY WAS PERFORMED	REMAINDER OF PREGNANCY AND DELIVERY	FATE OF MOTHER	FATE OF BABY
1	Shands,[29] 1929	25	Gr. iii P. ii	Idiopathic thrombocytopenic purpura	6½	Cesarean section performed at time of splenectomy	Recovery	Neonatal death (premature infant)
2	Bernstein and associates,[5] 1939	23	Gr. i P. 0	Idiopathic thrombocytopenic purpura	5	Premature delivery (7th month)	Recovery	Neonatal death (premature infant)
3	Phythyon and Lartz,[24] 1943	28	Gr. i P. 0	Idiopathic thrombocytopenic purpura	7½	Delivery 3 days after splenectomy	Recovery	Stillborn (premature and macerated infant)
4	Nordland and associates,[21] 1946	27	Gr. iii P. i	Idiopathic thrombocytopenic purpura	5	Term induction of labor	Recovery	Normal infant
5	Dinsmore and Dutlinger,[13] 1946	19	Gr. i P. 0	Idiopathic thrombocytopenic purpura	7	Cesarean section 8 days after splenectomy. Fetus dead before section	Recovery	Stillborn (premature and macerated infant)
6	Barnes and Doan,[3] 1948	21	Gr. i P. 0	Idiopathic thrombocytopenic purpura	7	Term pregnancy. Spontaneous delivery	Recovery	Normal infant
7	Barnes and Doan,[3] 1948	31	Gr. i P. 0	Idiopathic thrombocytopenic purpura	5	Term pregnancy. Outlet forceps delivery	Recovery	Normal infant
8	Polowe,[25] 1944	29	Gr. ii P. i	Secondary thrombocytopenic purpura (agnogenic myeloid metaplasia)	8	Term pregnancy	Recovery	Normal infant
9	Wolfe and Limarzi,[34] 1946 (Case of H. Alt)			Congenital hemolytic icterus	3½	Term pregnancy. Spontaneous delivery	Recovery	Normal infant
10	Barnes and Doan,[3] 1948	23	Gr. i P. 0	Congenital hemolytic icterus	4	Term pregnancy. Outlet forceps delivery	Recovery	Normal infant
11	McKenzie,[19] 1936	23	Gr. iii P. ii	Splenic anemia (first stage of Banti's syndrome)	3	Term pregnancy. Spontaneous delivery	Recovery	Normal infant

12	Rissmann,[26] 1916	30	P. iv	Banti's syndrome	7	Premature delivery 12 days after splenectomy	Recovery	Normal premature infant
13	Hesseltine,[15] 1930	42	Gr. iii P. ii	Banti's syndrome	3½	Hypertension and ascites in last trimester. Premature spontaneous delivery at 7½ mo.	Recovery after paracentesis	Normal premature infant
14	Serbin,[28] 1937	33	Gr. iv P. i	Banti's syndrome	4	Premature spontaneous delivery 3 weeks before term	Died 26 days after delivery. Cerebral hemorrhage and pneumonia	Stillborn (3 weeks premature)
15	Serbin,[28] 1937	23	Gr. ii P. 0	Banti's syndrome	4	Severe anemia in last trimester. Insertion of bag, version and extraction	Died 3 months after delivery. Thrombophlebitis, edema, ascites	Neonatal death (premature infant)
16	Kotschnew and Manenkow,[17] 1930 (Case of Savor, 1898)	31	Multipara	Spontaneous rupture of spleen	6	Term pregnancy	Recovery	Normal infant
17	Kotschnew and Manenkow,[17] 1930 (Case of Gemmel, 1912)	31		Spontaneous rupture of spleen	2		Died immediately after operation	Nonviable
18	Stretton,[32] 1926	37		Spontaneous rupture of spleen	5	Term pregnancy (presumed)	Recovery	Normal infant (presumed)
19	Smith and associates,[33] 1933	31		Spontaneous rupture of spleen	3	Albuminuria last 3 weeks. Term pregnancy. Spontaneous delivery	Recovery	Normal infant
20	Burnett and McMenemey,[8] 1935	43	Gr. xvi P. xv	Spontaneous rupture of spleen	8½	Cesarean section at time of splenectomy	Recovery	Normal infant
21	Sommer,[30] 1937	35		Spontaneous rupture of spleen	8	Cesarean section at time of splenectomy	Recovery	Twins: 1 stillborn; other neonatal death
22	Asteriades,[2] 1939	25	Gr. iii P. ii	Spontaneous rupture of spleen	9	Vaginal delivery at time of splenectomy	Recovery	Normal infant
23	Kotschnew and Manenkow,[17] 1930 (Case of Iwantschenko, 1928)	38	Multipara	Traumatic rupture of spleen	9	Term pregnancy. Spontaneous delivery 2 hours after splenectomy	Recovery	Stillborn
24	Bohler,[7] 1932	35		Traumatic rupture of spleen	7	Cesarean section at time of splenectomy	Recovery	Viable premature infant (presumed)

TABLE I—CONT'D

CASE	AUTHOR AND YEAR OF PUBLICATION	AGE IN YEARS	GRAVIDA; PARA	INDICATION FOR SPLENECTOMY	MONTH OF PREGNANCY IN WHICH SPLENECTOMY WAS PERFORMED	REMAINDER OF PREGNANCY AND DELIVERY	FATE OF MOTHER	FATE OF BABY
25	Asteriades,[2] 1939			Traumatic rupture of malarial spleen	7½	Chills and fever 2 days after operation. Quinine administered. Spontaneous premature delivery	Recovery	Neonatal death (premature)
26	Ireneus and associates,[16] 1945	27	Gr. i P. 0	Traumatic rupture of spleen	8¾	Spontaneous delivery 32 hours after splenectomy	Recovery	Stillborn
27	Bland-Sutton,[6] 1901	34	Gr. viii P. vii	Prolapsed spleen	2	Term pregnancy. Spontaneous delivery	Recovery	Normal infant
28	Meek,[20] 1907	32	Gr. i P. 0	Prolapsed spleen with torsion of pedicle	3½	Term pregnancy. Spontaneous delivery	Recovery	Normal infant
29	Davis,[12] 1908	20	Gr. iii P. i	Prolapsed spleen	4	Term pregnancy. Spontaneous delivery	Recovery	Normal infant
30	Barsalou,[4] 1922 (Case of James MacCann)	28		Prolapsed spleen	1 (presumed)	Term pregnancy. Spontaneous delivery	Recovery	Normal infant
31	Abell,[1] 1933	34	Gr. ii P. i	Prolapsed spleen	3½	Term pregnancy. Spontaneous delivery	Recovery	Normal infant
32	Abell,[1] 1933		Multipara	Prolapsed spleen	5		Died	Nonviable
33	(Cases which are not included elsewhere in this study)		P. i	Prolapsed spleen	2		Recovery	
34			P. iii	Prolapsed spleen	5		Died	Nonviable
35			P. v	Prolapsed spleen	5	Abortion 24 hours after operation	Died	Nonviable
36	Ottow,[23] 1936	27	Gr. ii P. i	Prolapsed spleen	3	Miscarriage 16 days after operation	Recovery	Nonviable
37	Barsalou,[4] 1922 (Case of D. Michaelowski)			Malarial splenomegaly	5	Term pregnancy. Spontaneous delivery	Recovery	Normal infant
38	Serbin,[28] 1937	30	Gr. ii P. i	Malarial splenomegaly	4	Term pregnancy. Low forceps delivery	Recovery	Normal infant

39	Asteriades,[2] 1939	30		Malarial splenomegaly	7	Term pregnancy	Recovery	Normal infant (presumed)
40	Asteriades,[2] 1939	29	Multipara	Malarial splenomegaly	8	Term pregnancy	Recovery	Normal infant (presumed)
41	Asteriades,[2] 1939	21	Gr. i P. 0	Malarial splenomegaly	7	Term pregnancy	Recovery	Normal infant (presumed)
42	Asteriades,[2] 1939	32		Malarial splenomegaly	4½		Died during operation	Nonviable
43	Chevalier,[9] 1938	17	Multipara	Torsion of malarial spleen	3	Term pregnancy (presumed)	Recovery (presumed)	Normal infant (presumed)
44	Asteriades,[2] 1939	27	Gr. v P. iv	Torsion of malarial spleen	6	Term pregnancy	Recovery	Normal infant (presumed)
45	Asteriades,[2] 1939			Torsion of malarial spleen	3	Term pregnancy (presumed)	Recovery (presumed)	Normal infant (presumed)
46	Asteriades,[2] 1939			Torsion of malarial spleen	5½	Term pregnancy	Recovery	Normal infant (presumed)
47	Asteriades,[2] 1939		Multipara	Torsion of malarial spleen	6	Spontaneous delivery. Question of being 1 month postmature	Recovery after pneumonia	Normal infant
48	Coenen,[10] 1910	30	Gr. vi P. v	Polycystic spleen	2	Term pregnancy (presumed)	Recovery	Normal infant (presumed)
49	Snyder,[31] 1943	37	Gr. ii P. 0	Polycystic spleen	4	Cesarean section at 9 months	Recovery	Normal infant
50	MacLeod and Maurice,[18] 1940	22		Rupture of a branch of the splenic artery	6½	Premature delivery	Recovery	Stillborn (premature and macerated infant)

Cases not mentioned in Table I because of insufficient data:

1. Nordland and associates[21] mentioned a case known to them at the Minneapolis General Hospital. Splenectomy for idiopathic thrombocytopenic purpura was performed in the course of pregnancy.
2. Barnes and Doan[3] cited a case of Trenis, Kunath, and Wilcox in which splenectomy was performed in the course of pregnancy for congenital hemolytic icterus.
3. Grossman[14] mentioned a case of idiopathic thrombocytopenic purpura during pregnancy in which splenectomy was performed. This has been cited by subsequent authors as another case of splenectomy in pregnancy. After careful study of the reports, we believe it to be the same case as that reported by Bernstein, Newman, and Hitzig.[5]
4. Barsalou[4] mentioned a case in which splenectomy in the course of pregnancy (indication not stated) was followed by normal delivery.

who weighed 3,370 grams had ecchymoses about the forehead and buttocks at birth. On October 17, the day after birth, the mother's platelet count was 243,000 per cubic millimeter of blood and the infant's platelet count was 58,000. Five days after birth, the infant's platelet count was 40,000 and the bleeding time was 5 minutes as opposed to a bleeding time of 2½ minutes five days before. A transfusion of 60 c.c. of blood was given to the infant. The next day the infant's bleeding time was 7 minutes but because the concentration of hemoglobin was 21.5 Gm. per 100 c.c., it was decided that another transfusion should not be employed. Eight days later (fourteen days after birth), the infant's platelet count was 28,000, and the bleeding time was 2 minutes. A sternal puncture on the infant showed normal formation of megakaryocytes. Five days later (nineteen days after birth) the platelet count was 140,000 and the infant was dismissed from the hospital.

The mother was unable to nurse her baby because of an inadequate supply of milk. In the puerperium, the mother's platelet count dropped to 28,000 and the bleeding time increased to 7 minutes but no purpuric manifestations occurred. The puerperium was otherwise uneventful.

This phenomenon of thrombocytopenia and an increased bleeding tendency in the infant of a mother with thrombocytopenic purpura has been considered in the literature.[11, 27]

Review of the Literature

The literature on splenectomy in the course of pregnancy may be best reviewed by presenting all of the cases that we have been able to discover (Table I). The average age of the women at time of splenectomy was 29 years and twelve diagnoses were represented in a listing of the conditions for which the operation was performed. Fifteen splenectomies were done for blood dyscrasias. Twenty-one operations were performed for traumatic and spontaneous rupture of the spleen and for ectopic spleen (wandering or prolapsed spleen). The average month of gestation in which splenectomy was performed was the fifth month. The outcome of the pregnancy from the maternal and fetal viewpoints is given in Table II. Seven of the fifty women (14 per cent) died and eighteen (36 per cent) of the fetuses on which we have information did not survive. If the nonviable fetuses are excluded, 27.3 per cent of the remaining fetuses did not survive. Of the term infants, 93.1 per cent lived. It is of interest to note that there were no maternal deaths in the pregnancies which went on to term and the two fetal deaths that occurred in these term patients were the fetuses of mothers splenectomized for splenic rupture which is, of course, extremely traumatic to the intrauterine environment. Only two maternal deaths occurred in those women splenectomized for blood dyscrasias—and both of these were in the Banti's syndrome group.

TABLE II. SUMMARY OF CASES REPORTED IN THE LITERATURE*

	OUTCOME FOR MOTHER		SURVIVAL OF CHILD	STILL-BIRTHS	NEONATAL DEATHS
	RECOVERY	DEATH			
Term pregnancy.—					
Vaginal delivery	29		27	2†	
Casarean section	2		2		
Premature pregnancy.—					
Vaginal delivery	6	2‡	2	3	3
Abdominal delivery	4		1	2	2
Abortions and miscarriages	1	5§		6	
Total	42	7	32	18	

*Data from Case 33 are not included in this table because of insufficient data on outcome for the child. The mother survived however.

†Infants of mothers whose spleens were removed for traumatic rupture.

‡Patients who underwent splenectomy for Banti's syndrome (deaths classified as obstetrical).

§Three of these deaths were surgical; two more probably were surgical.

Comment

No particular discussion of our five cases is necessary. The one maternal death occurred in a case in which either splenic anemia or chronic infectious splenomegaly was present. Three of the five infants survived. One of the deaths in infants may well have been due to the trauma of delivery and the remaining fetal death represented a stillbirth in the sixth month of gestation. Both deaths occurred in the fetuses of women who had undergone splenectomy for congenital hemolytic icterus. Our five cases in addition to the fifty cases listed in Table I and the three cases which we did not include in the table because of insufficient data bring the total number of known splenectomies in the course of pregnancy to fifty-eight. There were eight maternal deaths in this group and twenty fetal deaths.

Summary

The literature on splenectomy in the course of pregnancy has been reviewed and data on all cases of this interesting complication which we were able to find are presented in tabular fashion. In addition we have presented five previously unreported cases. When this operation is performed in the course of gestation for either idiopathic thrombocytopenic purpura or congenital hemolytic icterus, it appears that the outlook for the mother and infant is excellent if the pregnancy progresses to term. In cases of splenic anemia or Banti's syndrome, the outlook is not nearly so favorable. In three of the six recorded cases (including our case) in which splenectomy has been performed for this condition, maternal deaths occurred.

Concerning splenectomy in the course of pregnancy for the blood dyscrasias, which are the most common indication for this operation at present, we are in agreement with Barnes and Doan[3] who suggested that the indications for splenectomy in pregnancy are similar to those for splenectomy in the nonpregnant state and that the operation should be performed when critical hematologic indications are present. Gentleness at time of operation is perhaps the most important antiabortive measure that may be utilized in these cases but a medical antiabortive regimen in the postoperative period is also recommended.

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POSTOPERATIVE CERVICAL-VAGINAL HEALING IN RELATION TO POSTOPERATIVE TREATMENT

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CERVICAL conization and coagulation are the most commonly employed surgical procedures in office gynecology and vaginal plastic surgery is one of the most common hospital procedures in gynecology; healing must occur in spite of the pathogenic organisms normally present in the vagina. Chronic endocervicitis with its commonly associated erosion is seen in a very large number of multiparous patients and this postpartum complication is so common that there are many who recommend routine electrocoagulation of the cervix at the time of the examination six weeks post partum. Erosions of the cervix are common in virgin women in whom no specific bacterial offender can be demonstrated. The disease almost invariably accompanies the parasitic infections of the vagina and permanent cure of Trichomonas infection often depends upon eradication of a cervical focus.

Eradication of cervical infection depends upon complete destruction of all infected glands with sloughing and re-epithelization. Tissue healing following vaginal plastic surgery occurs in spite of bacterial contamination. Electrocoagulation, electroconization, and vaginal surgery are followed by a profuse purulent drainage lasting a few days to a few weeks, depending upon the amount of tissue coagulated and the extent of the vaginal surgery. The drainage usually has a foul odor which is quite annoying to the patient and occasionally results in a secondary vaginitis or vulvitis. Re-epithelization depends upon the cellular capacity for regeneration and a favorable vaginal environment for healing.

Bleeding following electroconization is a frequent complication and sometimes may be alarming. Although a sanguineous discharge from the coned cervix is expected and usually lasts several weeks, sudden and profuse hemorrhage occurs all too frequently on the eighth to twelfth day when the fibrino-leucocytic membrane covering the denuded cervix sloughs away, exposing relatively large vessels in the coned area. Although this complication is more common following conization than it is after coagulation, the latter is not without some danger. There have been reported at least 3 patients with severe hemorrhage requiring observation and packing following electrocoagulation, and at least one fatal hemorrhage has been reported from a cauterized cervix.

A third and relatively infrequent complication of conization and electrocoagulation is infection. This is believed to be due to a flare-up of an old pelvic infection rather than the result of the operation. No one has ever explained just how electrocoagulation arouses dormant bacteria to virulence in the mucosal or parametrial tissues but nevertheless this concept is widely held. It is more

likely that pathogenic bacteria find entrance to the parametrium through the denuded cervix, over which there is plastered a slough which provides the ideal culture for bacterial growth.

The vaginal douche has been considered by many to be contraindicated in the management of patients following electrocoagulation or electroconization. Mechanical displacement of the cervical slough is a potential hazard. Furthermore, the bacteriostatic effect of any vaginal douche is questionable because of the low concentration of the antiseptic agent in contact with tissue surface, and the very short time in which the douching solution remains in contact with the infected site.

It is true that the majority of patients treated by electrocoagulation or electroconization get satisfactory healing in four to five weeks when no postoperative care is given. However, from the standpoint of the patient's comfort during the postoperative period and particularly with the view to reducing the hazard of bleeding from the granulating cervix from which an infected slough has been dislodged, it would seem worth while to develop and institute a procedure which might reduce the hazard and decrease the patient's discomfort. Prevention of bleeding at the time of slough displacement depends upon complete thrombosis of the cervical vessels prior to the time the slough is dislodged. The fibrinolytic action of bacteria is well known and, if the bacterial content of the slough can be reduced, fibrinolysis will be reduced and a more firmly fixed thrombosis of the vessels will exist.

Various types of vaginal antiseptic agents have been used and there seems to be no great superiority of one over the other. Daily instillation of tincture of Mercresin reduces the purulent discharge and promotes more satisfactory healing. The daily intravaginal insertion of a tablet containing Diodoquin is likewise effective. Both of these preparations, however, have disadvantages: the tincture is difficult to instill at the cervical site and because of its alcohol content produces more discomfort, and the tablet being dry is slightly more painful to insert. It was decided, therefore, to undertake a control study using cetylpyridinium chloride ("Ceepryn")* suppositories.

Cetylpyridinium chloride vaginal suppositories contain a 1:1,000 concentration of the detergent germicide in a gelatin base, are easily inserted by the patient, melt promptly at body temperature, cover the entire cervical os and have a low surface tension which encourages intimate and prolonged contact of the highly efficient bactericidal agent. Their use has been reported[8] in the local therapy of cervicitis and cervical infections.

Postoperative Healing Following Electroconization of the Cervix

Inspection of the cervix and of the vaginal discharge was made daily in most patients and microscopic examination of the stained smear was done at regular intervals. The tabulation of results was based upon daily inspection

*This is a cationic detergent germicide with a potent bactericidal action, covering a wide range of pathogenic microorganisms, including yeasts and some protozoa, together with a high degree of detergence which gives a decided wetting or cleansing action.[1, 2, 3] Pharmacological and toxicological studies[4] have shown that it is relatively free from tissue toxicity when applied locally in therapeutic concentration to mucosal surfaces. Other studies[5, 6, 7] have demonstrated that the relation of activity on pathogenic bacteria and the tissue toxicity index is very favorable.

in most patients, but the longest period between examinations in the healing period was five days. Patients who were not examined and healing time recorded within five-day intervals were excluded from the study. Examinations were made over the convalescent period by the same physician. While the figures quoted in the tables may not be completely accurate, they are sufficiently so to permit evaluation.

The objective in this study was to determine whether or not the use of a vaginal suppository containing a detergent germicide would have any effect upon the postoperative course following electroconization. Accordingly, two groups of patients with various types of cervical pathology were subjected to electroconization. The diameter of the cone removed from the cervix was measured in all instances and attention was given to the duration of purulent drainage, the duration of sanguineous discharge, and the estimated time of re-epithelization in each group.

Effect of No Treatment (Table I).—

The patients in this group served as controls since they had no postoperative treatment. The age range in this group averaged 36 years. It will be seen from the table that in this group the purulent drainage lasted for 16 days and the sanguineous discharge, for 12 days. The estimated time of complete re-epithelization was 38 days.

TABLE I. CONIZATION OF CERVIX. POSTOPERATIVE COURSE IN CONIZATION—NO TREATMENT

PATIENT	AGE	CERVICAL PATHOLOGY	ESTIMATED DIAMETER OF CONE REMOVED (MILLIMETERS)	DURATION OF PURULENT DRAINAGE (DAYS)	SANGUINEOUS DISCHARGE (DAYS)	ESTIMATED TIME OF RE-EPITHELIZATION (DAYS)
GPN	29	Lacerated eversion	9	15	8	35
FOR	29	Erosion	5	9	4	21
TRS	20	Erosion	5	9	5	28
MYM	49	Cystic cervicitis	9	12	8	35
NEP	36	Lacerated endocervicitis	8	19	18	49
CEP	39	Cystic cervicitis	11	18	15	35
IRA	37	Lacerated eversion	13	20	22	42
BRE	41	Lacerated eversion	13	22	16	50
ECL	40	Lacerated eversion	10	20	15	42
AME	38	Cystic cervicitis	9	12	10	40
JPT	42	Lacerated eversion	12	17	12	38
Average:	36		9	16	12	38

Effect of Cetylpyridinium Suppositories (Table II).—

A group of 10 patients were treated with cetylpyridinium chloride suppositories. The age range in this group averaged 35 years. Postoperative care consisted solely in the insertion by the patient high into the vaginal vault of two suppositories daily. In this group the purulent drainage persisted for 8 days and the sanguineous discharge for 5 days, and the estimated time of complete re-epithelization was 21 days. In one case (E. N. T.) profuse bleeding occurred on the ninth postoperative day and persisted only on this day.

TABLE II. CONIZATION OF CERVIX. POSTOPERATIVE COURSE IN CONIZATION EFFECT OF CETYLPYRIDINIUM CHLORIDE SUPPOSITORIES

PATIENT	AGE	CERVICAL PATHOLOGY	ESTIMATED DIAMETER OF CONE REMOVED (MILLIMETERS)	DURATION OF PURULENT DRAINAGE (DAYS)	SANGUINEOUS DISCHARGE (DAYS)	ESTIMATED TIME OF RE-EPITHELIZATION (DAYS)
ENT	37	Lacerated endocervicitis	12	19	15	21
VAG	26	Erosion endocervicitis	8	5	4	23
CEP	29	Lacerated eversion	15	6	6	23
PRE	45	Lacerated eversion	12	8	5	25
FTR	44	Laceration eversion endocervicitis	11	12	10	26
MEC	28	Endocervicitis erosion	10	5	2	18
TRS	35	Cystic cervicitis	12	6	2	20
TRP	32	Laceration endocervicitis	13	7	4	18
PAR	40	Laceration endocervicitis	14	6	5	19
TCL	30	Endocervicitis erosion	7	3	0	15
Average:	35		12	8	5	21

Postoperative Healing Following Electrocoagulation of the Cervix

The same general procedures as outlined above were followed in the postoperative care following electrocoagulation. Again, as in conization, a group of 10 patients received no postoperative therapy.

Effect of No Treatment (Table III).—

TABLE III. COAGULATION OF CERVIX. POSTOPERATIVE COURSE AND HEALING TIME IN RELATION TO POSTOPERATIVE TREATMENT

NO TREATMENT

PATIENT	AGE	CERVICAL PATHOLOGY	ESTIMATED DEPTH OF COAGULATION (MILLIMETERS)	DURATION OF PURULENT DRAINAGE (DAYS)	SANGUINEOUS DISCHARGE (DAYS)	ESTIMATED TIME OF RE-EPITHELIZATION (DAYS)
AOU	26	Cystic cervicitis	4	17	8	24
URM	36	Lacerated cysticitis	6	18	12	22
LCR	42	Lacerated cysticitis	5	19	8	27
MCV	45	Laceration endocervicitis	7	22	6	31
MBR	22	Erosion	4	12	2	23
UCL	31	Endocervicitis	8	19	7	31
MOU	38	Eversion	9	22	10	34
GTM	39	Endocervicitis	8	19	5	24
CTL	23	Erosion endocervicitis	6	12	3	27
DRP	29	Lacerated endocervicitis	8	22	12	Did not heal (40)
Average:	33		7	18	7	30

The average age of the 10 patients in the control group who received no treatment was 33 years. The estimated depth of coagulation varied from 4 to 9 mm., with an average of 7 mm. The average duration of purulent drainage was 18 days and of the sanguineous discharge, 7 days. The average time of re-epithelization was 30 days.

Effect of Acid Douche (pH 3.5) (Table IV).—

Ten patients were advised to use an acid douche (pH 3.5) daily following electrocoagulation of the cervix. Results are shown in Table IV. The age range in this group averaged 30 years. The depth of the area coagulated averaged 7 mm. The duration of purulent drainage following electrocoagulation averaged 13 days in all patients. A sanguineous discharge was seen on an average of 4 days in this group. The average time for re-epithelization was 19 days. None of the patients treated in this group had any complications resulting from the douche.

TABLE IV. COAGULATION OF CERVIX. POSTOPERATIVE COURSE AND HEALING TIME IN RELATION TO POSTOPERATIVE TREATMENT
ACID DOUCHE (pH 3.5)

PATIENT	AGE	CERVICAL PATHOLOGY	ESTIMATED DEPTH OF COAGULATION (MILLIMETERS)	DURATION OF PURULENT DRAINAGE (DAYS)	SANGUINEOUS DISCHARGE (DAYS)	ESTIMATED TIME OF RE-EPITHELIZATION (DAYS)
MUC	28	Erosion endocervicitis	5	12	4	17
ARS	31	Cystic cervicitis	8	12	4	20
TNR	40	Eversion endocervicitis	7	10	3	16
MBN	29	Cystic cervicitis	6	12	2	18
JSR	29	Lacerated endocervicitis	9	14	4	21
VNA	41	Eversion endocervicitis	7	17	5	24
FCM	25	Endocervicitis	5	8	1	16
GHI	22	Erosion endocervicitis	4	11	4	16
HCV	32	Cystic cervicitis	6	13	5	18
RZJ	29	Eversion endocervicitis	8	16	4	21
Average:	30		7	13	4	19

Effect of Alkaline Douche (pH 7.5) (Table V).—

The same number of patients (10) were advised to use an alkaline douche in order to compare it with the acid douche in healing of the cervix following electrocoagulation. The age range of these patients averaged 29 years. The average depth of coagulation was not as deep as in the acid group, averaging only 5 mm. Duration of purulent drainage averaged 15 days and sanguineous discharge, 6 days. The average time required for healing was 31 days. In one patient in this group (E. C. A.), healing was incomplete on the twenty-seventh day and we were unable to observe the patient further to determine the exact healing time.

Effect of Cetylpyridinium Chloride Suppositories (Table VI).—

A group of 11 patients were instructed to use cetylpyridinium chloride suppositories following electrocoagulation of the cervix, the procedure being the same as that used following electroconization. The average age reported in

this group was 33 years. The depth of coagulation in this group ranged from 4 mm. to 10 mm. with an average of 7 mm. A purulent drainage was present for an average of 4 days. Sanguineous discharge lasted an average of only 2 days. An average of 15 days was required for re-epithelization. One patient (A. C. H.) in this group had a chronic endocervicitis complicated by gonorrhea. Her estimated complete re-epithelization time was 19 days.

TABLE V. COAGULATION OF CERVIX. POSTOPERATIVE COURSE AND HEALING TIME IN RELATION TO POSTOPERATIVE TREATMENT

ALKALINE DOUCHE (pH 7.5)

PATIENT	AGE	CERVICAL PATHOLOGY	ESTIMATED DEPTH OF COAGULATION (MILLIMETERS)	DURATION OF PURULENT DRAINAGE (DAYS)	SANGUINEOUS DISCHARGE (DAYS)	ESTIMATED TIME OF RE-EPITHELIZATION (DAYS)
ECA	28	Cystic cervicitis	7	16	9	27 (Incom)
TRL	29	Eversion endocervicitis	6	20	10	40 (Incom)
LMQ	30	Erosion endocervicitis	4	15	5	31
ING	22	Erosion endocervicitis	5	16	6	29
CHR	34	Lacerated endocervicitis	8	22	8	34
ADE	27	Cystic cervicitis	6	17	7	31
ANT	29	Eversion endocervicitis	3	9	2	27
PLA	33	Erosion endocervicitis	4	9	2	30
GEN	35	Endocervicitis	6	14	4	32
ALB	21	Erosion	4	9	1	33
Average:	29		5	15	6	31

TABLE VI. COAGULATION OF CERVIX. POSTOPERATIVE COURSE AND HEALING TIME IN RELATION TO POSTOPERATIVE TREATMENT

CETYLPYRIDINIUM CHLORIDE SUPPOSITORIES

PATIENT	AGE	CERVICAL PATHOLOGY	ESTIMATED DEPTH OF COAGULATION (MILLIMETERS)	DURATION OF PURULENT DRAINAGE (DAYS)	SANGUINEOUS DISCHARGE (DAYS)	ESTIMATED TIME OF RE-EPITHELIZATION (DAYS)
GOD	29	Erosion cysticitis	8	3	0	13
INT	44	Lacerated eversion	9	7	2	17
ABO	19	Erosion	4	1	0	11
ACH	36	Endocervicitis (G.C.)	7	5	2	19
EPT	25	Lacerated endocervicitis	9	6	0	18
LOA	29	Cystic cervicitis	8	4	0	13
IRR	48	Lacerated eversion	7	3	3	15
PLA	39	Cystic cervicitis	8	5	2	13
EUT	22	Erosion	4	0	0	10
SYP	30	Eversion laceration	10	8	5	20
MOR	37	Cystic cervicitis	8	5	2	16
Average:	33		7	4	2	15

Postoperative Healing Following Vaginal Plastic Surgery

There were 50 patients upon whom vaginal plastic surgery was done, anterior and posterior colpoperineorrhaphy being performed in all. Twenty-five of these patients were given no vaginal medication following operation and the other 25 patients received the bacteriostatic suppository inserted twice daily into the vagina.

It is much more difficult to estimate on a comparative basis the relative healing times in patients subjected to vaginal surgery than it is in those following electroconization and electrocoagulation of the cervix. The extent of the surgical procedures necessarily varies. Daily inspection is not justified on purely surgical grounds and the discomfort which would be occasioned by the introduction of the speculum serves to make accurate evaluation in relation to postoperative care extremely difficult.

It was the impression of this observer, however, that the group of patients treated with vaginal suppositories were much more comfortable—certainly the foul vaginal drainage was practically eliminated. Edema about the suture line of the perineum was less and the patients were more comfortable. This is purely a clinical impression, however, as definite criteria on which comparison could be made is lacking.

Summary

An attempt has been made to evaluate the effect of different modes of therapy upon the postoperative course of electroconization and electrocoagulation of the cervix. In each case the results of therapy were compared to those in an untreated group used as controls.

Table VII represents a summary of the postoperative course of the two groups of patients following electroconization of the cervix. In the untreated group, the estimated diameter of the cone removed was 9 mm., the average duration of purulent discharge was 16 days, and of sanguineous discharge, 12 days. The average estimated time of re-epithelization was 38 days. In the group treated by inserting two cetylpyridinium chloride suppositories high up in the vaginal vault each day, the diameter of the cone removed was 12 mm. The suppositories were effective in reducing the duration of purulent drainage to 8 days and of sanguineous discharge to 5 days, and the estimated time of re-epithelization to 21 days.

TABLE VII. CONIZATION OF CERVIX. COMPARISON OF POSTOPERATIVE COURSE AND HEALING TIME IN RELATION TO POSTOPERATIVE TREATMENT

SUMMARY*

	NUMBER OF PATIENTS	AGE	ESTIMATED DIAMETER OF CONE REMOVED (MILLIMETERS)	DURATION OF PURULENT DRAINAGE (DAYS)	SANGUINEOUS DISCHARGE (DAYS)	ESTIMATED TIME OF RE-EPITHELIZATION (DAYS)
No treatment	11	36	9	16	12	38
Cetylpyridinium chloride suppositories	10	35	12	8	5	21

*Represents averages shown in Tables I and II.

In the group undergoing electrocoagulation of the cervix in various types of cervical pathology (Table VIII), in those who received no treatment the depth of coagulation reached 7 mm., the duration of purulent discharge averaged 18 days, and of sanguineous discharge, 7 days, while the time of re-epithelization averaged 30 days. In the group using an acid douche (pH 3.5), the estimated depth of coagulation was 7 mm., the duration of purulent drainage 7 days, of

sanguineous discharge, 4 days, and the estimated time of re-epithelization was reduced to 19 days. In the group using an alkaline douche (pH 7.5), the duration of purulent discharge was 15 days, of sanguineous discharge, 6 days, and the estimated time of re-epithelization was 31 days. In the group using cetylpyridinium suppositories daily, the average duration of purulent drainage was reduced to 4 days and of sanguineous discharge to 2 days. The estimated time of re-epithelization was reduced to 15 days.

TABLE VIII. COAGULATION OF CERVIX, COMPARISON OF POSTOPERATIVE COURSE AND HEALING TIME IN RELATION TO POSTOPERATIVE TREATMENT

SUMMARY*

	NUMBER OF PATIENTS	AGE	ESTIMATED DEPTH OF COAGULATION (MILLIMETERS)	DURATION OF PURULENT DRAINAGE (DAYS)	SANGUINEOUS DISCHARGE (DAYS)	ESTIMATED TIME OF RE-EPITHELIZATION (DAYS)
No treatment	10	33	7	18	7	30
Acid douche (pH 3.5)	10	30	7	13	4	19
Alkaline douche (pH 7.5)	10	29	5	15	6	31
Cetylpyridinium chloride suppositories	11	33	7	4	2	15

*Represents averages shown in Tables III, IV, V, and VI.

Conclusions

In studying the effect of different postoperative procedures following electroconization, electrocoagulation of the cervix, and vaginal plastic operation it was found that the duration of purulent drainage and sanguineous discharge was reduced by some procedures and the time of epithelization could be reduced by certain types of therapy. An acid douche was apparently effective in reducing the time of drainage and discharge and in hastening re-epithelization, whereas the use of an alkaline douche daily showed no effect. The daily use of two cetylpyridinium chloride suppositories was very effective in reducing the duration of purulent drainage and sanguineous discharge, as well as the time of re-epithelization and healing.

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THE DEVELOPMENT OF A VAGINAL CYTOLOGY LABORATORY: ITS PRECISION AND SIGNIFICANCE*

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A NEW principle was introduced into the field of uterine cancer detection when Papanicolaou[4] suggested (1928) that cancer cells were shed by uterine malignancies and could be detected in smears of vaginal fluid. This concept of exfoliation of neoplastic cells from the uterus has been elaborated by Papanicolaou and Traut[22] in New York (1943) and amply confirmed by Meigs, Graham, and their associates[19] in Boston, Gates and Warren in Boston,[37] Ayre in Montreal,[23] and many other careful workers since that time.

The use of this method has opened an avenue of early diagnosis which was almost completely unrecognized before this era: the possibility of detection of early cervical and endometrial cancer in an asymptomatic, preclinical phase. In the past, biopsy techniques have required the presence of a lesion to biopsy. Cytologic methods, while they still require biopsy for confirmation, enrich the survey opportunities to include apparently perfectly healthy, asymptomatic women, with cervices that are normal to clinical examination.

The interpretation of vaginal and cervical smears requires training in cytologic techniques and it also requires time. This method cannot be used successfully, therefore, by part-time personnel drafted occasionally from the pathology laboratory routine. The pathologist untrained in this special field cannot hope to compete in accuracy with cytologic personnel engaged solely in this work.

We wish to present the work of our laboratory in the study of our first one thousand cases, to illustrate the significance and precision one should expect from this method as an aid to gynecological diagnosis and as a formidable weapon in any cancer detection type of activity in asymptomatic women. This study may be considered the work of a developing laboratory.

Method of Study

We have obtained material from two sources: (a) patients upon whom suspicion of uterine cancer has been cast in our gynecological tumor clinic or wards; (b) patients without gynecological symptoms who have come to our general hospital diagnostic clinic for nonpelvic disorders. In this manner we have pursued our dual purpose of evaluating the cytologic method as a gynecological diagnostic aid and also as a possible public health measure.

We have studied vaginal and cervical smears from these patients and stained them according to the Papanicolaou method. We have taken multiple smears on many patients and we have studied them in a uniform manner, adhering to rigid nuclear criteria of malignancy.

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We have limited this report to the first one thousand cases on which we have adequate follow-up studies. Patients with suspicious or positive smears who have been lost to us before biopsy confirmation have been excluded. We have also omitted several cases which are still in process of investigation. In general, we believe sufficient time has elapsed to allow for stabilization of our figures. We have obtained biopsy or curettage specimens for tissue confirmation on all patients with such an indication. This tissue correlation is always necessary in estimating the accuracy of the cytology technique. We have been very rigid in our tissue standards, since we are reporting a relatively large number of unsuspected cases detected by cytology methods and because we believe tissue studies are a valuable aid in evaluating cells with abnormal but not diagnostic features so that we may continually narrow down and more sharply define the various cytologic categories of abnormality.

Table I presents a general survey of our results. It serves to illustrate the accuracy we have attained and presents a brief analysis of our errors.

TABLE I. VAGINAL CYTOLOGY

Total patients studied	1,000
Asymptomatic and screened private patients	419
Total sets of smears	1,039
Accuracy of cytologic diagnosis	97.7%
Patients with proved malignancy	72
Patients with borderline malignancy (basal-cell hyperplasia)	2
Per cent incidence	7.4%
Cases with positive smears	63
Per cent accuracy	85.1%
False-negative analysis:	
Cases with suspicious smears	7
Adenocarcinoma	3
Adenocarcinoma post radiation	1
Adenoacanthoma	1
Intraepithelial carcinoma of cervix	3
Squamous-cell carcinoma of cervix	2
Squamous-cell carcinoma of cervix, post radiation	1
False-positive diagnoses	12
Per cent incidence	1.2%

Of our first one thousand cases, approximately 40 per cent were asymptomatic and had no evidence of malignancy on physical examination. We encountered 72 malignant lesions in this study; two other patients with positive smears showed changes on biopsy which could not be called cancer with certainty, but they were of a borderline character of suspicious activity, sometimes termed basal-cell hyperplasia, and pathologist and clinician agreed that hysterectomy should be done as a prophylactic measure. Of these 74 patients, 63 showed positive smears.

For statistical purposes we have called all Class III (suspicious) smears negative; these cases have been classified as errors unless examination of subsequent smears gave a definitely positive result. Thus, of eleven errors, seven had suspicious smears at some examination, leaving only four with totally negative smears. Of these four cases, two were adenocarcinoma of the corpus, one an adenoacanthoma, and one an intraepithelial carcinoma of the cervix. Careful review of these slides failed to reveal any cells suggesting malignancy.

It is interesting to note that in each of the cases having suspicious smears not subsequently shown positive, there were either symptoms or physical findings suggesting malignancy. For this reason, in two cases only were repeat

smears obtained before therapy was offered; in both cases the second examination was negative, both were adenocarcinoma of the corpus. Of the remaining five errors, two were intraepithelial carcinoma, two were postradiation recurrent squamous-cell carcinoma of the cervix, and one was an untreated squamous-cell carcinoma of the cervix.

Re-examination of false positive smears revealed that in two instances the cytologic changes were due to radiation effects following therapy for squamous-cell carcinoma of the cervix, and seven were certainly errors of judgment: Errors were due to misinterpretation of large atypical histiocytes in one case, large atypical endocervical cells in one case, atypical cells from squamous metaplasia in three cases, and from inflammatory reaction in two cases. All of these would be considered Class II (negative) if reported today.

In two other cases, however, cytologic changes apparently due to inflammatory reaction so closely resemble malignant alteration that an error seems almost inescapable. In both of these smears there are cells containing large, hyperchromatic nuclei of a character commonly seen in truly positive smears.

Table II is a comparison of our accuracy in the first and second half of this study. It illustrates the improvement one may expect with self-education and the greater precision obtained with respect to cervical carcinoma than we have found possible with corpus cancer.

TABLE II. ACCURACY OF VAGINAL CYTOLOGY

	FIRST 500 CASES			SECOND 500 CASES			TOTAL CASES		
	NO. OF CASES		PER CENT ACCURATE	NO. OF CASES		PER CENT ACCURATE	NO. OF CASES		PER CENT ACCURATE
	POSITIVE	NEGATIVE		POSITIVE	NEGATIVE		POSITIVE	NEGATIVE	
Squamous carcinoma of cervix	24	3	88.8	7	0	100.0	31	3	91.1
Intraepithelial carcinoma of cervix	2	2	50.0	10	1	90.9	12	3	80.0
Adenocarcinoma	14	3	82.3	3	2	60.0	17	5	77.2
Sarcoma	1	0	100.0	0	0	—	1	0	100.0

The increased accuracy in the diagnosis of intraepithelial carcinoma of the cervix, which is particularly notable, may be attributed to two factors: (1) increased use of the cervical as well as the vaginal smears, (2) additional experience. The relatively large number of cases of intraepithelial carcinoma in this group may be explained by our discovery of several asymptomatic unsuspected cases on routine cytologic examination, and by our selection of cases for cytologic study; since our personnel was limited, we preferred biopsy of clinically visible lesions in order that more time might be available for screening and for less obvious but suspected cases. During the first 500 cases, on the other hand, we routinely smeared all malignancies available, largely as one means of extending our educational experience.

With respect to the accuracy of diagnosis of adenocarcinoma of the corpus, we can add little to previously published reports, but reiterate that this detection phase seems unlikely to reach the same degree of accuracy as that of cervical cancer. The problem here stems from the common occurrence of well-differentiated malignant lesions of the endometrium whose exfoliated cells closely resemble those of normal or hyperplastic endometrium.

The unique and significant aid one can expect from the cytologic method is further illustrated by cases presented in Table III, those primarily diagnosed by this technique. Some were asymptomatic, others, with minimal symptoms, unsuspected of malignancy until these tests were positive.

TABLE III. PRIMARY CYTOLOGIC DETECTION (TO JAN. 1, 1949)

NO. OF SCREENED CASES, 419
NO. OF CASES PRIMARILY DIAGNOSED BY SMEAR, 15
TOTALLY ASYMPTOMATIC CARCINOMA CASES, 8

	CASE NO.	AGE IN YEARS	CLINICAL DIAGNOSIS	SYMPTOMS	ORIGINAL BIOPSY	FINAL DIAGNOSIS
1.	I. M. 916966	44	Cervical erosion	Mild menopausal menorrhagia	Normal cervix	Intraepithelial carcinoma
2.	V. B. 792082	39	Chronic salpingitis	Pain; one episode of bleeding	Basal-cell hyperplasia	Intraepithelial carcinoma
3.	E. B. 886860	53	Granulation tissue in vault	Pain; sanguineous discharge	Unsatisfactory	Adenocarcinoma of cervix
4.	G. H. 911339	43	Cervical erosion	Right upper quadrant pain	Intraepithelial carcinoma of cervix	Intraepithelial carcinoma
5.	M. L. 905046	40	Chronic cervicitis	Headaches	Squamous carcinoma of cervix, early	Squamous carcinoma of cervix
6.	J. N. 913163	37	Cervical erosion	None	Negative	Intraepithelial carcinoma
7.	M. R. 603124	32	Cervical erosion	Midcycle spotting	Suspicious	Intraepithelial carcinoma
8.	C. W. 701035	68	Postmenopause bleeding. Cause?	Vaginal bleeding, five years	Repeatedly negative	Squamous carcinoma of cervix
9.	E. W. 883797	45	Post radiation carcinoma of cervix	None	Squamous carcinoma of cervix	Squamous carcinoma of cervix
10.	S. S. Pvt.	38	Normal cervix	None	Squamous carcinoma of cervix	Squamous carcinoma of cervix
11.	M. E. 809599	57	Atrophic cervix	Dizziness and fatigue	Carcinoma of cervical stump, early	Squamous carcinoma of cervix
12.	S. T. 909313	29	Retroperitoneal sarcoma	Weakness, extremities	--------	Retroperitoneal sarcoma
13.	J. O. 925502	24	Cervicitis salpingitis	Vaginal discharge	Basal-cell hyperplasia	Basal-cell hyperplasia
14.	R. P. 931204	42	Cervical erosion	None	Basal-cell hyperplasia	Basal-cell hyperplasia
15.	B. H. 931011	58	Normal	None	Intraepithelial carcinoma of cervix	Intraepithelial carcinoma

Of the 1,000 cases reported here, 419 were routine screening examinations. Among these, eight totally asymptomatic unsuspected cases of malignancy were found. We also found recurrent or residual malignancy in two patients following radiation therapy who presented no clinical evidence of recurrence. Five other patients in this group presented minor gynecological symptoms but they were of a nature which failed to arouse suspicion of cancer after pelvic examination. This group included one patient with brownish discharge, another with one episode of slight intermenstrual spotting, another with mild increase in the amount of menstrual flow without any other menstrual aberration. In none of these patients was there any finding on pelvic examination which suggested malignancy, although cervical erosion occurred with the usual frequency. One patient had had postmenopausal bleeding for five years, but repeated curettage and numerous biopsies failed to disclose the carcinoma which was ultimately disclosed by cytologic methods. A brief presentation of several of these cases may serve to illustrate the importance of cytologic detection for these patients.

CASE 1.—No. 343. M. L., aged 40 years, entered the hospital because of chronic headache, sinusitis, and multiple allergies. During the course of her general work-up, she was examined by a gynecologist who found a lacerated cervix with an erosion and chronic cervicitis.

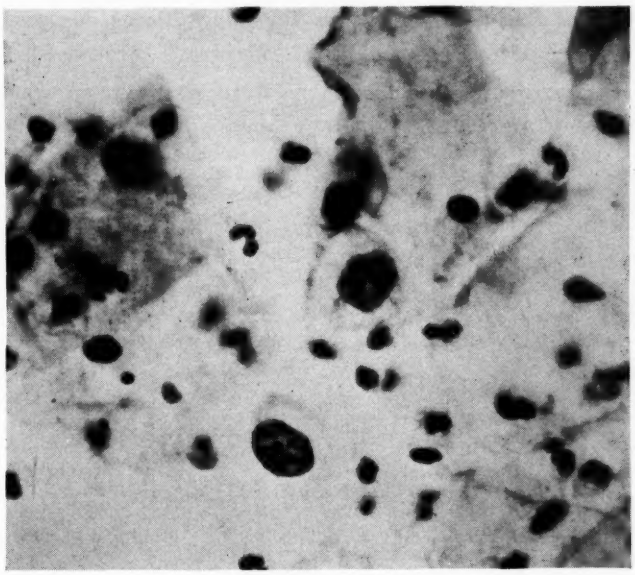

Fig. 1.—Several malignant cells in the center of a field containing normal squamous cells and leucocytes.

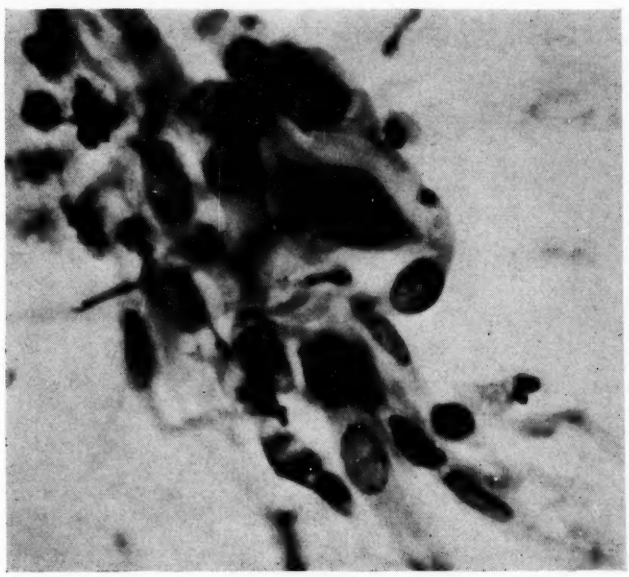

Fig. 2.—Cluster of malignant cells. Many are spindle shaped.

The patient's menstrual history was normal, she had no pelvic symptoms. A routine cytologic examination was made on April 14, 1948, and it was Class IV (positive); repeat smears on April 19, 1948, were also Class IV. Biopsy on April 20, 1948, showed intraepithelial carcinoma of the cervix with areas of early invasion (Fig. 1).

CASE 2.—No. 488. J. N., aged 37 years, was an asymptomatic patient with a small cervical erosion which had been treated by cauterization under the care of her local physician several days prior to cytologic examination. A scraping taken June 1, 1948, from this area was reported Class V (positive). On re-examination June 9, 1948, the erosion had healed. Smears at this time were Class III only. Biopsy disclosed a small area of intraepithelial carcinoma (Fig. 2).

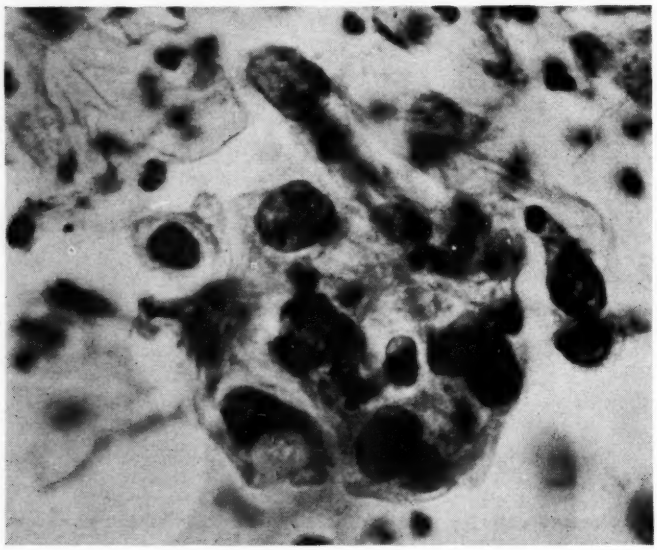

Fig. 3.—Group of clearly malignant cells illustrating clumping of chromatin, heavy nucleoli, and accented nuclear membrane.

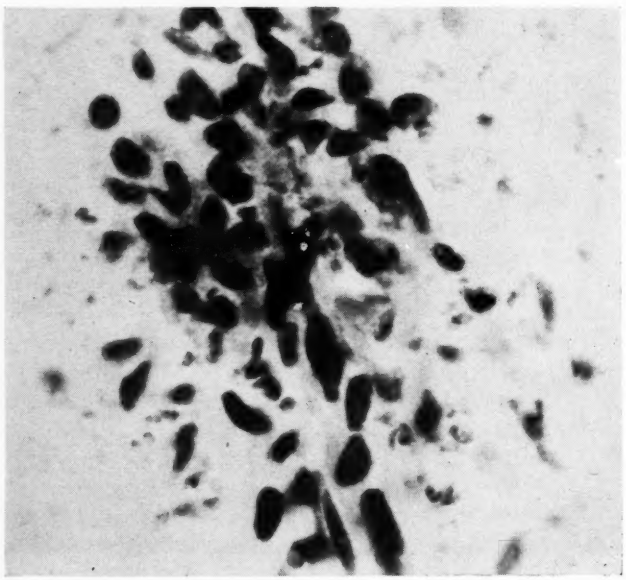

Fig. 4.—Clump of markedly abnormal cells with very heavy chromatin. Much variation in size and shape of cells.

CASE 3.—No. 522. G. H., a 43-year-old woman came to the diagnostic clinic complaining of right upper quadrant pain and constipation of eight months' duration. She thought the condition was aggravated at the menses. A diagnosis of chronic cholecystitis was made.

Routine screening smears taken June 17, 1948, were reported Class III (suspicious) and repeat smears were requested. These were taken July 15, 1948, and reported positive. A biopsy taken the same day revealed intraepithelial carcinoma of the cervix (Fig. 3).

CASE 4.—No. 914. B. H., aged 58 years, para ii, gravida iv, was seven years past a normal menopause; she had had no postmenopausal bleeding or other pelvic symptoms. This patient was examined by a staff gynecologist after routine vaginal smears were reported positive elsewhere. This examination revealed an innocent-appearing cervical erosion but no other abnormality. Smears studied in our laboratory were reported Class V (positive), and a coning biopsy of the squamous-columnar junction showed intraepithelial carcinoma of cervix (Fig. 4).

CASE 5.—No. 206. The case of C. W. is interesting not because this patient was asymptomatic, for she had had postmenopausal bleeding for five years. During this time, cervical biopsies and dilatation and curettage on five occasions failed to disclose malignancy of corpus or cervix. On Feb. 20, 1948, smears were taken and reported Class IV positive; repeat smears on April 8, 1948, were again positive. Following this finding the patient, a 68-year-old diabetic, was admitted to the hospital where biopsy showed epidermoid squamous-cell carcinoma of the cervix (Fig. 5).

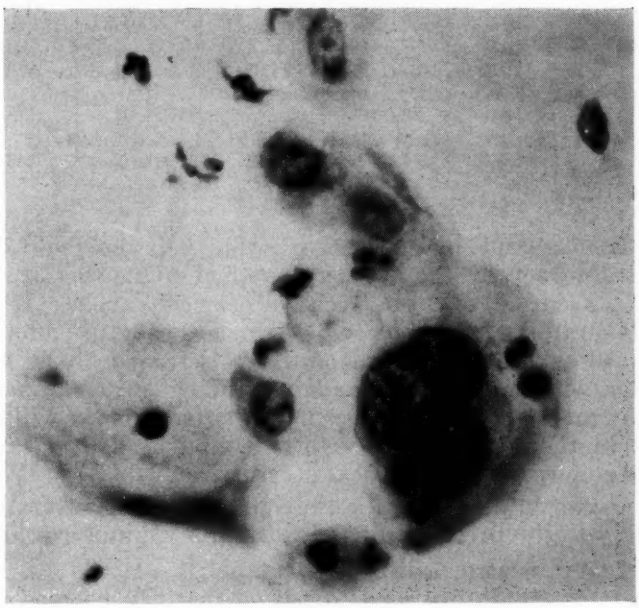

Fig. 5.—Evident tumor cells stand out clearly in background of normal vaginal cells. Cytoplasm difficult to define because of grouping, but nuclear-cytoplasmic ratio is considerably increased.

Comment

Since no reporting standard has been set up with respect to accuracy of cell-smear examination, it is difficult to compare the published work of various laboratories. Some groups have reported their work on the basis of cases studied, as we have done and as Papanicolaou did in his early papers; some have used a single set of smears as their unit, others have reported their accuracy on the basis of individual smears. The published studies also vary with respect to the use of total accuracy in some and separation of corpus and cervix cases in others, with positive and negative accuracy also entering as a statistical factor.

Table IV presents a compilation of the reported cytologic accuracy of several large laboratories.

TABLE IV. CYTOLOGIC ACCURACY, PUBLISHED REPORTS

AUTHOR	YEAR	ALL UTERINE MALIGNANCIES	CARCINOMA OF CERVIX	INTRAEPITHELIAL CARCINOMA OF CERVIX	CARCINOMA OF CORPUS	REPORTING UNIT
Papanicolaou and Traut[22]	1943 1945	93.90%	96.8%	----	90.7%	3,014 patients
Meigs, Graham, Fremont-Smith, Janzen, and Nelson[30]		89.70%	----	----	----	1,015 patients
Isbell, Jewett, Allen, and Hertig[39]	1947	90.45%	97.5%	----	83.4%	1,000 patients
Scheffey, Rakoff, and Hoffman[48]	1948	68.95%	70.2%	----	66.7%	500 individual smears
Jones, Neustaedter, and Mackenzie[29]	1945	92.10%	----	----	----	434 patients
Ulfelder[49]	1948	------	89.9%	----	79.4%	3,630 patients
Mackenzie, Wetchler, Dubois, and Neustaedter[45]	1948	98.00%	96.0%	----	100.0%	112 patients with malignancy
Robertson[47]	1948	87.50%	----	----	----	1,262 smears
Foote and Li[41]	1948	------	----	77.8%	----	18 patients
Gates and Warren[37]	1947	77.00%	----	----	----	1,300 patients
Graham, Sturges, and McGraw[43]	1948	------	91.0%	----	----	3,800 patients
Kernodle, Cuyler, and Thomas[44]	1948	92.00%	----	----	----	1,709 patients
Sloane Hospital, this report	1949	87.07%	91.1%	80.0%	77.2%	1,000 patients

It is clear from a study of such reports that it is possible to attain a clinically significant accuracy by the cytologic method. One should not be satisfied with less than an accuracy of 90 per cent in cervical cancer. It seems evident, too, that most laboratories will achieve a lesser accuracy in endometrial cancer; this finding is not unexpected for a lesion which is frequently an extremely well-differentiated one with individual glands appearing quite normal. We do not believe that early or intraepithelial carcinomas of the cervix will lag far behind invasive cancer in their susceptibility to detection by cell smears for the histological surface abnormality is identical in both.

We have become impressed with the importance of several factors which contribute notably to the precision of the work of a vaginal cytology laboratory:

1. The careful training of full-time personnel.
2. Restriction of laboratory load to a level that can be reasonably handled. Adequate time for proper examination must be emphasized.
3. Study of cervical as well as vaginal smears.
4. Repeat smear examination of patients with suspicious but not clearly diagnostic smears.
5. Complete biopsy control. We have been helped immeasurably by the use of the endocervical biopsy curette[51] in obtaining circumferential cervical samples for correlation studies.
6. Adherence to rigid cytologic criteria.

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STATUS OF MEMBRANES AND UTERINE CONTRACTION CHARACTERISTICS AS CRITERIA FOR CLINICAL SUCCESS OR FAILURE IN THE USE OF PITOCIN BY CONTINUOUS INTRAVENOUS DRIP FOR INDUCTION OF LABOR*

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THE judicious use of posterior pituitary extracts by intravenous drip is a recent innovation in obstetrics which has much to commend it. The effects are prompt, easily controlled, and are said to be clinically advantageous as compared to intramuscular administration (Hellman, Harris, and Reynolds, 1950; Stone, 1950; Theobald, 1948, and Jeffcoate, 1948). When the action of the uterus is recorded by the multichannel tokodynamometer, the advantages of Pituitrin by intravenous drip over its administration by intramuscular administration are best seen. It has been reported that low, controlled doses of the drug can be given which evoke activity predominantly in the fundus as compared to more caudal parts of the uterus (Hellman, Harris and Reynolds, 1950). This, it has been observed (Reynolds, Bruns and Hellman, 1948), is particularly desirable in effecting delivery, since the first stage of labor in the human being is characterized by a gradient of diminishing uterine activity from above, downward. In this way, the resisting lower parts of the uterus, including the cervix, are passively distended and prepared by stretching for the second stage of labor. Conditions favoring induction of labor during intravenous drip administration of Pitocin have not been described, however. This is the subject of the present paper.

The characteristics of the gradient of activity are determinable by suitable recording techniques. With these, the intensity of contractions in grams of force for a given area of uterus may be measured, along with the duration in seconds of the contractions, and their frequency. An approximate estimate of the work performed by a part of the uterus in a given period of time (work index) may be made by multiplying the factors of intensity and duration of contractions. The gradient of work may be judged by determining the ratio of work done in one part of the uterus to that in another by relating the two work indices to each other (i.e., work index in fundus divided by work index in lower uterus).

With these facts as a basis, a study has been made of the contraction characteristics of the uterus as useful criteria for clinical success or failure when

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Pitocin is used by intravenous drip* for induction of labor. Thirty-four observations are reported on the use of Pitocin in twenty-four patients not in labor. All were in the thirty-ninth or fortieth week of pregnancy except one hypertensive woman in whom four attempts were made to induce labor in the thirty-sixth and thirty-seventh weeks of pregnancy. In addition, continuous intravenous drip of Pitocin has been used in attempted induction of labor and in cases of uterine inertia without records of uterine contractions having been made. A clinical report of this experience will be reported separately (Lubin, Reynolds, Tisdall, Waltman, and Delson, in press†), although attention has been directed already to the potential hazard of associated uterine spasm upon the fetal heart rate when Pitocin is used by intravenous drip even in high dilution (Lubin, 1949). The dosages and rates of administration are shown in Tables I and II.

Results

Although longer control and experimental periods were recorded in every instance, attention for purposes of this study has been focused upon the twenty-minute period immediately preceding and immediately following the administration of Pitocin. By so doing, the initial uterine contraction characteristics associated with clinical success and clinical failure in the induction of labor have been studied. Clinical success was considered to be achieved when, within a matter of several hours or less, cervical dilatation progressed and the uterus subsequently emptied itself of its contents. Clinical failure was considered to result when, in the absence of initiation and progress of cervical dilatation at the time of drug administration, labor did not commence for more than three hours after withdrawal of the Pitocin. The status of the membranes was controlled in some instances by rupturing them artificially just prior to the administration of Pitocin, soon after Pitocin was begun, or by not rupturing them. Membranes were ruptured in seven cases, four of these before Pitocin. Membranes were ruptured artificially in three cases prior to Pitocin and in four cases after Pitocin administration was begun. The distribution of these among the clinical successes and failures is shown in Tables I, II, and III.

The data of this study are presented in Tables I and II. In Table I, the contraction characteristics of the uterus observed in the twelve cases of clinical success in induction of labor are presented. Similarly, in Table II, the contraction characteristics of the uterus observed in twenty-two failures in induction of labor are given. The data do not require further review here, since what appear to us to be the principal results of this study are shown in Tables III, IV, and V. This will be discussed briefly below. Records of uterine activity were obtained by means of a two-channel strain gage tokodynamometer employing a magnetic oscillographic ink-writing recorder. This was described in an earlier study by us on the nature of Braxton Hicks contractions (Delson, Lubin, and Reynolds, 1950).

Analysis of Data

Membrane Status and Induction of Labor.—Table III shows clearly that rupturing of the membranes just before or after administering Pitocin by intravenous drip is related to clinical success in induction of labor. Eleven of twelve successes had ruptured membranes. In contrast, only three of fourteen with ruptured membranes failed to go into labor and but one in twenty with membranes intact went into labor during intravenous Pitocin drip without mechani-

*Acknowledgment is made to the Abbott Laboratories for furnishing the Venopak and the prepared solutions of dextrose used in this study.

†Am. J. Obst. & Gynec.

TABLE I. SUMMARY OF DATA IN CLINICAL SUCCESSES IN PITOCIN INDUCTIONS OF LABOR BY INTRAVENOUS DRIP

PATIENT NO.	CERVICAL DILATATION	PITOCIN DOSE (1:5,000 I.V. DRIP)	ACTIVITY BEFORE PITUITRIN						ACTIVITY AFTER PITUITRIN						EVALUATION OF CHANGES WHICH MIGHT BE FAVORABLE TO DELIVERY	CLINICAL OBSERVATIONS
			I		D		F	G OR WF	I		D		F	G OR WF		
			f.	l.	f.	l.			f.	l.	f.	l.				
176	–	60 d.p.m.	61	0	36	0	24	2,196	89	0	44	0	30	3,916	I,D,F,G	MRS before Pit.
182	2-3 cm.	20-50 d.p.m.	76	18	63	12	9	22.2	64	9	41	13	12	22.4	F	MRS after Pit.
184	2 cm.	60 d.p.m.	22	9	37	21	24	4.3	33	12	33	17	29	5.3	I,D,F,G	MRS after Pit.
189	2 cm.	1:10,000 107 d.p.m.	39	0	39	0	11	1,521	38	0	29	0	12	1,102	F	MRA after Pit.
188	1-2 cm.	52 d.p.m.	14	0	16	0	33	224	39	15	40	28	24	3.7	I,D	MRA after Pit.
190	1-2 cm.	30-80 d.p.m.	18	0	35	0	6	630	31	0	46	0	18	1,426	I,D,F,G	MRA after Pit.
194	3-4 cm.	60-30 d.p.m.	61	22	41	37	12	3.0	34	1	52	5	24	353.6	D,F,G	MRA after Pit.
197	1-2 cm.	38 d.p.m.	34	22	95	53	9	2.8	72	7	79	15	12	5.4	I,F,G	MRA before Pit.
173	2-3 cm.	50 d.p.m.	37	0	51	0	9	1,887	42	0	40	0	12	20,160	I,F,G	MRA before Pit.
195	3 cm.	30 d.p.m.	51	47	45	54	15	0.9	60	28	44	27	21	3.5	I,D,F,G	MRA before Pit.
171	2 cm.	25 d.p.m.	19	7	24	23	16	2.8	26	3	36	3	16	104	I,D,G	MRS inertia
196	3-4 cm.	1:10,000 112 d.p.m.	21	0	32	0	9	672	26	19	39	41	24	1.24	I,D,F	MI inertia

Explanation of Symbols:

d.p.m. = drops per minute

I = intensity, grams of force

D = duration of contraction, seconds

F = frequency, contractions per hour

G or Wf = Gradient of activity, or Work Index in fundus

$$\frac{(I \times D \text{ in fundus})}{(I \times D \text{ in lower uterus})}$$

f. = fundus

l. = lower uterus

MRA = membranes ruptured artificially

MI = membranes intact

MRS = membranes ruptured spontaneously

TABLE II. SUMMARY OF DATA WHERE CLINICAL FAILURE WAS ENCOUNTERED FOLLOWING THE USE OF PITOCIN BY INTRAVENOUS DRIP*

PATIENT NO.	CERVICAL DILATATION	PITOCIN DOSE (1:5,000 I.V. DRIP)	ACTIVITY BEFORE PITUITRIN						ACTIVITY AFTER PITUITRIN						EVALUATION OF CHANGES WHICH MIGHT BE FAVORABLE TO DELIVERY	CLINICAL EVALUATION
			I		D		F	G OR WF	I		D		F	G OR WF		
			f.	l.	f.	l.			f.	l.	f.	l.				
175	0	1:10,000 60 d.p.m.	16	0	36	0	9	576	66	0	42	0	18	2,772	I,D,F,G	MI
	0	1:5,000 60-150 d.p.m.	98	0	60	0	3	5,880	28	12	41	22	8	4.35	F	MI
		60 d.p.m.	32	0	31	0	3	1,292	34	0	30	0	3	1,020	—	MI
	–	60 d.p.m.	0	0	0	0	0	0	0	0	0	0	0	0	—	MI
	0	60-150 d.p.m.	0	0	0	0	0	0	0	0	0	0	0	0	—	MI
174	1 cm.	1:5,000 110 d.p.m.	39	0	46	0	8	1,794	47	0	66	0	7	3,102	I,D,F,G	MI
	–	60-120 d.p.m.	26	0	35	0	9	910	25	0	35	0	15	875	F	MI
183	2 cm.	50-60 d.p.m.	90	0	67	0	6	6,030	61	0	75	0	12	4,575	D,F	MI twins
	2 cm.	90 d.p.m.	60	0	60	0	3	3,600	42	0	52	0	6	2,184	F	MI
187	–	36-80 d.p.m.	38	0	51	0	9	1,938	64	0	48	0	21	3,072	I,F,G	MI
170	–	1:1,000 25 d.p.m.	37	0	48	0	15	1,776	28	0	43	0	15	1,204	—	MI
181	1 cm.	50-150 d.p.m.	18	0	40	0	3	720	24	12	47	28	9	3.36	I,D,F	MRS before P't.
179	1-2 cm.	50-60 d.p.m.	29	0	54	0	9	1,566	29	0	37	0	10	1,073	F	MI
178	0	60-200 d.p.m.	37	0	108	0	6	3,996	43	0	43	0	10	1,849	I,F	MI
193	0	56 d.p.m.	0	0	0	0	0	0	0	0	0	0	0	0	—	MI
172	2 cm.	60 d.p.m.	51	0	105	0	6	5,355	47	0	56	0	12	2,632	F	MI
	1 cm.	60 d.p.m.	32	0	42	0	6	1,344	27	0	36	0	7	972	F	MI
	1 cm.	60-90 d.p.m.	0	0	0	0	0	0	0	0	0	0	0	0	—	MI
	1 cm.	60-90 d.p.m.	0	0	0	0	0	0	0	0	0	0	0	0	—	MI
	1 cm.	60-90 d.p.m.	0	0	0	0	0	0	0	0	0	0	0	0	—	MRS del. 2 days
191	1-2 cm.	30-48 d.p.m.	22	0	44	0	7	968	15	0	36	0	10	540	F	MI face present.
192	1-2 cm.	1:10,000 30 d.p.m.	0	0	0	0	0	0	0	0	0	0	0	0	—	MRS before Pit.

*See Table I for explanation of symbols.

cal interference either spontaneously or artificially. With what contraction characteristics is successful induction associated? This is shown in the analysis which follows.

TABLE III. EFFECT OF MEMBRANE STATES ON UTERINE CONTRACTION CHARACTERISTICS AFTER INTRAVENOUS PITOCIN DRIP

STATUS OF MEMBRANE	CLINICAL SUCCESSES	CLINICAL FAILURES
Intact	1	19
Ruptured before Pitocin	2	3
Ruptured after Pitocin	9	0

Chi square = > 2000
P = < 0.001

Intensity of Contractions.—As shown in Table IV, the intensity of contractions in the successes and failures stand in marked contrast to each other. In the successes, 75 per cent of the instances showed contractions of increased intensity within the first twenty minutes after starting the administration of Pitocin by intravenous drip. In the failures, on the contrary, about 74 per cent of the cases showed there was no effect of the drugs on intensity or the contractions were of diminished intensity. A prompt increase in intensity upon beginning of the injection is, therefore, a favorable sign for clinical success in the induction of labor, but not an infallible one.

Duration of Contractions.—A similar result was observed with respect to the effect of Pitocin on the duration of the contractions. In two-thirds of the successes, contractions were of increased duration. In the failures, 82 per cent of the attempts to induce labor met with no effect upon the duration of contractions or actually made them shorter. We conclude, therefore, that increased duration of contractions upon commencing Pitocin administration by intravenous drip is a favorable indication of successful induction, but not an essential one.

Gradient of Work Index in the Fundus.—In the group of clinical successes, two-thirds of the cases showed increased fundal dominance within the first twenty minutes of Pitocin administration. In the group of clinical failures, only 14 per cent of the attempts showed such an increase in fundal dominance, as evidenced by the calculated gradient coefficient or index of work activity in the fundus. Eighty-six per cent of the failures failed to show such an effect. Thus we conclude that an increase in fundal dominance is a frequent but not infallible early sign of successful induction by intravenous drip of Pitocin.

TABLE IV. SUMMARY OF EFFECT OF PITOCIN BY INTRAVENOUS DRIP ON UTERINE CONTRACTION CHARACTERISTICS IN ATTEMPTED INDUCTION OF LABOR

	CONTRACTION CHARACTERISTICS							
	INTENSITY		DURATION		GRADIENT OR WORK INDEX		FREQUENCY	
CHANGE IN QUALITY OF BRAXTON HICKS CONTRACTIONS	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
1. *Successful Inductions.*—								
a. Effect favoring delivery	9	75	8	66.6	8	66.6	10	83.3
b. Effect adverse to delivery	3	25	4	33.4	4	33.4	2	16.7
2. *Unsuccessful Attempts.*—								
a. Effect favoring delivery	5	27.8	4	17.7	3	14.1	13	54.5
b. Effect adverse to delivery	13	54.5	14	64.6	15	68.2	5	27.8
c. No contractions and none induced	4	17.7	4	17.7	4	17.7	4	17.7

Frequency of Contractions.—Intravenous drip of Pitocin for the induction of labor causes an increase in the frequency of contractions more often than not. In 83 per cent of the successes and 54 per cent of the failures such an effect was observed. In the failures, 17.7 per cent showed no Braxton Hicks activity prior to contractions, and no activity was induced. When there is activity of the uterus prior to injection, an increase in frequency is a common observation, therefore. Thus we conclude that an increase in frequency of contractions is related in no important way to the successful outcome of the attempted induction of labor. The other characteristics of the contractions described above are, accordingly, more significant features of the uterine contractions that indicate the outcome of the procedure.

Frequency of Favorable Labor Characteristics and Successful Induction.—When one stresses, as above, the individual features of the contraction characteristics and the outcome of the attempted induction, one fails to consider what is happening simultaneously to the other characteristics of the contraction pattern as well. The result of such consideration of the data offered in Tables I and II is shown in Table V. In this table, the number of characteristics is considered to be three since frequency of contraction has been shown above to be unrelated to induction. These are intensity, duration, and fundal dominance (i.e., gradient or work index). The proportion of cases showing changes favorable to labor in two or three of the characteristics favorable for labor was 83.3 per cent in the successful inductions, and 18.2 per cent in the unsuccessful attempts at induction of labor. By contrast, the proportion of cases showing none or only one of the characteristics favorable to labor upon administration of Pitocin is 16.7 per cent in the successful induction group and 81.8 per cent in the unsuccessful inductions. When two or three characteristics favorable to labor were present in the first twenty minutes, ten out of fourteen such cases went into labor. The Chi-square test applied to these data yields a value of 13.7, a *highly significant* value. Clearly, therefore, when two or three of the characteristics of uterine contractions now known to be favorable to labor appear within the first twenty minutes after intravenous drip of Pitocin is begun the chances are four and one-half to one that labor will ensue. Conversely, when less than two of such characteristics favorable to labor appear in the first twenty minutes the chance of induction is but about one in five.

TABLE V. FREQUENCY DISTRIBUTION OF CASES EXHIBITING ACTIVITY CHARACTERISTICS CONSIDERED TO BE FAVORABLE TO THE INDUCTION OF LABOR UPON INTRAVENOUS DRIP ADMINISTRATION OF PITOCIN. CHARACTERISTICS ARE INTENSITY, DURATION, AND FUNDAL DOMINANCE

NO. OF CONTRACTION CHARACTERISTICS FAVORABLE TO LABOR IN ANY ONE CASE	CLINICAL SUCCESSES		CLINICAL FAILURES	
	NO.	PER CENT	NO.	PER CENT
3	4	83.3	2	18.2
2	6		2	
1	0	16.7	2	81.8
0	2		16	

Chi square = 13.7
P = < 0.01

Summary

1. Attempts to induce labor near term by continuous intravenous drip administration of Pitocin were made thirty-four times in twenty-four patients in whom records of uterine contractions were made by means of a two-channel strain gage tokodynamometer.

2. Successful induction of labor was achieved in twelve patients.

3. Successful induction required mechanical rupture of the membranes, artificially or spontaneously in eleven of twelve cases, and failed in only three of fourteen cases.

4. It was found that:

(a) a prompt increase in intensity of contractions is a favorable sign for clinical success in the induction of labor, but not an infallible one;

(b) increased duration of contractions is a favorable indication of successful induction, but not an essential one;

(c) an increase in fundal dominance is a frequent but not infallible early sign of successful induction by intravenous drip administration of Pitocin;

(d) an increase in the frequency of contractions is related in no important way to the successful outcome of an attempted induction of labor.

5. The characteristics of intensity, duration, and fundal dominance bear a definite relation to the successful induction of labor.

6. When two or more of these characteristics increase upon commencement of intravenous drip administration of Pitocin, the chances of labor ensuing is about 4.5 to 1. When less than two such characteristics of uterine contractions increase, the chance that labor will ensue is about 1 to 5. The statistical significance of these ratios is $P = <0.01$.

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AN OBJECTIVE EVALUATION OF HYPNOSIS IN OBSTETRICS

Preliminary Report

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WE ARE coming to realize more and more that a number of the difficulties and ills which human beings suffer are caused by their beliefs, traditions, and customs. For example, it is a belief that a woman should and will suffer great pain in childbirth. The girl hears this throughout the years and it has a great suggestive effect upon her. The result is that she will likely suffer pain at childbirth simply because she is conditioned to expect it. That childbirth pain is not necessary is indicated by the experience of women in some other parts of the world where this expectation of pain does not exist. Such women look upon childbirth as a natural function which is not expected to cause any more discomfort than any other physiological function of the body. In their experience, childbirth is quick and painless. Since the patient is conditioned to expect pain, the physician is forced to use methods to try to alleviate this pain.

Obstetricians have for many years been seeking a method of pain relief for the parturient woman. This search has led to the development of a multiplicity of techniques utilizing drugs of many kinds, orally, parenterally, and locally. All of these methods, with the exception of the use of local anesthesia, suffer from the same drawback and that is that they are not entirely safe for both the mother and baby. The obstetrician in his search for the ideal obstetrical analgesic and anesthetic has, however, overlooked what the authors feel is a very important consideration in the care of the pregnant and parturient women, and that is her proper psychological preparation for her lying-in period. Agreeing that patients have been given the best of physical care and preparation for their labors, we must admit that due to a lack of time and frequently of desire, we have not been preparing our patients mentally for a physical experience that should be one of the high points in the life of any woman.

Following the publication in 1944 of Grantly Dick Read's book, *Childbirth Without Fear,* there has been an increasing interest shown by a number of men in this technique of pain relief for the patient in labor. Thoms and Goodrich[1] recently, among others, have corroborated Read's work.

Inasmuch as Read's technique depends on the use of education, relaxation, and suggestion, and inasmuch as hypnosis also depends on relaxation and suggestion, it was felt that if the Read technique was carried a step further and a trance state induced, the results could be improved.

Hypnosis in medicine and surgery is, of course, not new. Many surgical procedures, both major and minor, have been performed with the use of hypnosis as the only anesthetic. The difficulty has always been that the lay person has felt that there is something mysterious about the procedure and as a result has been fearful about submitting himself to it. Today, hypnosis is an integral part of the psychological sciences and a great deal of investigation is now being carried on in this field.

In one of the earliest and most complete investigations done on the use of hypnosis in obstetrics in 1922, Schultze-Rhonhof[2] achieved a success of 89.5 per cent in seventy-six cases. He states that the disadvantages of the procedure are mainly the time necessary to condition the patient for delivery and the presence of someone at the time of labor who has been trained in the technique of handling these patients. These two disadvantages, as he points out, can very easily be eliminated.

Kroger,[3, 4] in two articles written in 1943, described the use of hypnosis both in obstetrics and for the treatment of dysmenorrhea. He was enthusiastic in citing the advantages of the method and gave no contraindications to its use. Greenhill[5] in commenting on this paper stated, "It is unfortunate that most physicians consider hypnotism as charlatanism, because hypnosis is exceedingly useful in various fields of medicine—it should be used more extensively in obstetrics and gynecology."

Kroger,[6] in another paper titled, "The Treatment of Psychogenic Disorders by Hypnoanalysis," describes the use of hypoanalysis, particularly for the common complaint of frigidity in women, with excellent success.

Wolberg,[7] in speaking of the use of hypnosis in dentistry, obstetrics, and surgery, states, "The anesthesia under hypnosis is profound and except for major surgical procedures is as effective as chemical anesthesia." He states further, "Obvious advantages are the ease of administration, the immediate removal of anesthesia when desired, and the absence of postoperative reactions to the anesthetic." In speaking of its use in obstetrics, Wolberg states, "Where the patient responds positively to these (hypnotic) suggestions, a total absence of pain results and postpartum discomfort is minimal."

LeCron and Bordeaux[8] also discuss the use of hypnosis in obstetrics and gynecology in their recent book, *Hypnotism Today*.

Personal communications[9-14] from a number of physicians have been variable in their reaction to the use of hypnosis in obstetrics, ranging in enthusiastic approval of the technique to a noncommittal acceptance of it as another possible method of analgesia.

The older literature is replete with descriptions of the use of hypnosis in a large variety of ailments both in general medicine and obstetrics and surgery, but to date there has been no objective attempt to evaluate it in its true perspective and from an unbiased point of view.

It has appeared desirable, therefore, to make a more extended study using no selection of cases except that the patient be willing to cooperate in this experiment. This procedure would then give a better idea of what the physician may hope to accomplish by the use of this technique on the general run of patients. By using a fairly large number of subjects, we may also assess the advantages and disadvantages of hypnosis, and come to a conclusion concerning the practicality of the method.

Material

The subjects in this experiment were partly private and partly clinic patients. No attempt was made to start these patients on the training at any specified period of their pregnancy. Nor was any attempt made to hold con-

stant the number of training periods given to the patient. Therefore, the training periods of approximately thirty minutes each ranged from two to as many as eight, with an average of four per patient. Some subjects were started as early as the second month of pregnancy and others as late as the eighth month. The average for the group was the seventh month.

In the training periods an attempt was made to get as deep a stage of hypnosis as possible. There are, of course, large individual differences in this respect from the few who do not go into the hypnotic condition at all to those who go into the deepest somnambulistic trance. There is no adequate objective method of determining the depth of hypnosis except to give the subject a series of tests involving the induction of catalepsy, anesthesia, hallucination, and amnesia. The giving of more than the very simplest of these tests is not desirable from the professional point of view because it is difficult for the subject to understand the relationship, for example, between having an hallucination and having a baby; therefore, the subject may feel that she is being made an experimental guinea pig to satisfy the curiosity of the physician and some subjects tend to resent this. Further, unless time is taken in reassuring the patient, she may be frightened when she experiences some of the phenomena which can be produced in the hypnotic stage; such a situation is obviously unfortunate from a psychological point of view. For such reasons, no systematic attempt was made to determine the depth of trance in our subjects. One or two were obviously not influenced at all. Others were apparently in the somnambulistic state. In doing an experiment of this kind, one is torn between the desire to have very careful controls and measurements, and the desire to make the situaiton as nearly as possible what the physician will meet in his everyday practice. We have allowed the latter desire to dominate our procedure in the present study. The phenomenon which we stress most with all the patients was relaxation. This is a condition which can be quite easily induced in the hypnotic state, even in the lighter trance, and the relaxation is frequently much more complete than the subject can immediately accomplish otherwise.

The techniques of inducing the hypnotic trance and the conditioning process will not be discussed in this report as all of the methods that we have used have been adequately described in many previous publications. It is our feeling that any acceptable method of trance induction serves the purpose.

In this study we have been particularly concerned with objective indication of the effects of the training. If we were to rely solely on the subjective estimates by the patients we would have an almost 100 per cent favorable response. The patients felt that the training made parturition easier for them. It is a little difficult to understand upon what basis a primipara would make such a statement except possibly that she found her labor not so difficult as she expected it to be. Although these subjective reports have some value we would prefer to rest the case for the training on objective evidence. In order to do this, it was necessary for comparative purposes to have a group of patients who have not been trained. This group, called the control group, was obtained by pulling records at random from the hospital files. From the hospital records then certain data were secured for both the trained, called the experimental group, and the control group.

Results

In Table I are given data which show the comparability of these two groups in reference to certain factors which may have some bearing upon labor. An inspection of Table I indicates that our experimental and control groups were quite comparable except for the fact that there were 62 per cent of primiparas in the experimental group and 48 per cent in the control.

TABLE I. COMPARISON OF EXPERIMENTAL AND CONTROL GROUPS

	NUMBER OF SUBJECTS	MEAN AGE (YEARS)	NUMBER OF PRIMIPARAS	MEAN NUMBER OF PREGNANCIES	MEAN NUMBER OF LIVING CHILDREN	MEAN WEIGHT OF BABY
Experimental	100	24.2	62	1.62	.55	7.1 lb.
Control	88	24.9	42	2.15	1.03	7.3 lb.

Still using data from the hospital records we can now compare these two groups in an effort to determine objectively the effectiveness of the training given the experimental group. In Table II, the pertinent comparisons are made.

TABLE II. COMPARISON OF EXPERIMENTAL AND CONTROL GROUPS WITH REFERENCE TO LABOR

	FIRST STAGE	SECOND STAGE	THIRD STAGE	MEAN AMOUNT OF DEMEROL GIVEN DURING LABOR
Experimental	8.32* hours	35.8 min.	8.8 min.	103.5 mg.
Control	10.31 hours	34.8 min.	7.4 min.	123.6 mg.

*The record of one experimental patient is omitted from these calculations. She was a primipara who had a first-stage labor of 72 hours with a breech delivery. During all that period, however, she took only 100 mg. of Demerol. No comparable case is included in the control group.

An inspection of Table II indicates that the mean length of the first stage is 1.99 hours less for the experimental group. This is a statistically significant difference at the 3 per cent level; i.e., a difference of that magnitude could be expected to occur by chance only three times in one hundred.

The variability of the first stage of labor for the experimental group is also less than for the controls. This is indicated by the fact that the standard deviation for the experimentals is 5.05 hours and for the controls 7.12 hours. A difference of this magnitude would be expected to occur by chance only once in one thousand times.

The data with reference to Demerol also show a difference in favor of the experimental group. This difference of 20.1 mg. could be expected to occur about nine times out of one hundred by chance alone. Some of the controls were given other sedative drugs which have not been included in our calculations.

It is generally stated that the labor of the primipara is, on the average, longer than that of multipara. That this is true is indicated by the data in Table III.

TABLE III. COMPARISON OF FIRST STAGE LABOR IN PRIMIPARA AND MULTIPARA

	NUMBER OF PRIMIPARAS	NUMBER OF MULTIPARAS	FIRST STAGE MEAN IN HOURS		
			PRIMIPARAS	MULTIPARAS	DIFFERENCE
Experimental	62	38	9.65	6.17	3.48*
Control	42	36	12.88	7.96	4.92†

*Probability of occurrence by chance: 1 in 1,000.
†Probability of occurrence by chance: 8 in 10,000.

Since we had 14 per cent more primiparas in our experimental group than in our control, it is likely that the difference of 1.99 hours is less than it would have been had the percentage of primiparas in the two been equal. This possibility is made more probable when we examine Table IV which shows us the effectiveness of the training upon the primipara as compared with the multipara.

Table IV indicates that the training is more effective for the primipara than for the multipara. It reduced the time of the first stage for the former on the average of 3.23 hours and the latter by 1.79 hours.

TABLE IV. COMPARISON OF THE REACTION TO THE TRAINING OF THE PRIMIPARAS TO THE MULTIPARAS IN TERMS OF THE MEAN LENGTH OF THE FIRST STAGE OF LABOR

	MEAN HOURS FIRST STAGE	MEAN DIFFERENCE IN HOURS
Primiparas.—		
Experimentals	9.65	3.23*
Controls	12.88	
Multiparas.—		
Experimentals	6.17	
Controls	7.96	1.79†

*Probability of occurrence by chance: 3 in 100.
†Probability of occurrence by chance: 4 in 100.

Comment

There is no doubt that spectacular results can be obtained in some patients by the use of hypnosis during parturition but these cases are not representative of the gravid women in general. The ability to go into a hypnotic state is complicated and involves many personality factors in the patient as well as skill on the part of the hypnotist. At the present time it is possible to put only about 20 per cent of normal adult individuals into the deepest hypnotic condition. It is with such subjects that one is likely to get the most spectacular results.

But we do not have to seek only these outstanding cases in order to establish appreciable benefits from prenatal hypnotic training. A mean reduction of 20 per cent in length of the first stage of labor with a minimum of drug is certainly to be desired and especially so when the patients subjectively feel that they have received much help.

These results, we feel, could be much improved if the obstetrical nursing staffs were adequately trained in handling patients under hypnosis. A patient in the hypnotic state must be handled differently from one under the influence of a sedative. She should be spoken to quietly and gently. She should not be questioned unless necessary. She should be told of any manipulation by the nurse or physician before the manipulation is done, and while it is in progress suggestions of relaxation and sleep should be constantly given the patient. Undue noise should be eliminated, such as cries from the delivery room and complaints of other patients. These are not too difficult measures to take, but when one is accustomed to working with patients under drug sedation it becomes easy to disregard precautions against these small irritations, irritations, nevertheless, which help to make it difficult for the patient to remain in the hypnotic state since the patient is always conscious in hypnosis.

In deliberating upon the results of an experiment of this sort, a consideration which immediately arises from the physician is that of the practicability of the method used in gaining the results. In the present case the chief point to be considered is that of the time involved in the prenatal training. Is the physician willing to give a minimum of four half-hour sessions to each patient for this training? Probably most obstetricians would feel that they could not afford the time in their routine practices. We hope to continue our experiment to determine if we cannot get as good or better results by training the patients in groups of perhaps six or eight individuals. Here we will use techniques which have been reasonably successful in the production of so-called mass hypnosis.

We hope also to get other objective measures of the effectiveness of the treatment. For example, we can attach an apparatus to the bed which

measures the movements of the patient. Presumably, the more relaxed a patient is, the less movement she will make in the bed. Possibly this can also be called an indirect measure of labor discomfort. The greater the discomfort during contractions the more likely is the patient to move during such contractions. In a fairly well-relaxed patient, the record from the machine gives a good indication of the frequency and duration of the contractions as evidenced by her gross bodily movements.

In an effort further to determine the relationship between the ability to be hypnotized and personality and thus the possibility of predicting the value of hypnosis for any patient, we are now having patients take the Minnesota Multiphasic Personality Evaluation Test both before being given any hypnotic conditioning and subsequently following delivery. This determination will then also be an aid in objectively evaluating the use of hypnosis in obstetrics.

Summary and Conclusions

Prenatal training in hypnosis can be of definite benefit to patients during parturition. It may give very significant relief from the discomfort of labor even in cases which do not show the spectacular results sometimes obtained, which are so fond to the heart of many of those who dabble with hypnosis. An average reduction of two hours in length of the first stage of labor with a minimum of drug would seem to be a result which is eminently desirable. It is this stage which is so monotonous and fatiguing to the patient. If this stage is prolonged, minutes seem like hours, especially if through undue tension and apprehension each contraction brings severe discomfort.

The great difficulty in the use of hypnosis is the time and effort which are required on the part of the physician to give the prenatal training. Another difficulty is that the hospital staff is not trained to deal with patients in the hypnotic state. If we can overcome the first difficulty by mass training, it should not be hard to train adequately nurses and other members of the hospital staff in the proper care of such patients.

If these two difficulties can be overcome, we believe that the method will be practicable and holds significant promise toward the relief of the discomforts of parturition, with no possible risk to the patient or her baby.

The authors wish to express their thanks to Mrs. Marie Hopkins, Superintendent of Maternity Hospital, Minneapolis, for her cooperation in this study.

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DELAYED GASTRIC EMPYTING TIME IN LABOR*

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DURING the past ten years, in the city of Philadelphia alone, there have been at least twelve maternal deaths attributable directly to the aspiration of vomitus during obstetrical anesthesia. In reviewing the literature, Meurlin,[10] Abramson,[1] and Mendelson[9] report maternal deaths of a similar nature occurring in other parts of the country. Those patients who do not die from suffocation from aspiration of gastric contents, either during or after anesthesia, have serious postpartum complications. Laryngeal-bronchial obstruction or massive atelectasis may develop from aspiration of solid food substances, or an asthma-like syndrome may result from liquid aspiration. All these deaths and complications are probably preventable.

On the obstetrical service of the Woman's Hospital, we observed that about 40 per cent of all patients vomited either during or immediately following obstetrical inhalation anesthesia. The vomitus often consisted of food ingested several hours prior to the time of delivery. This fact suggested a delay in the emptying time of the stomach during labor, and prompted the following study.

Object of Study

The object of this study was to determine the variation, if any, in the gastric emptying time of women in labor. Two preliminary studies were necessary, the first to ascertain whether or not pregnancy alone was a significant factor, the second to note the effect of sedation on gastric motility.

Technique

A group of seventy-five patients was selected from our prenatal clinic, and the studies were carried out over a period of four months. All were either gravida i or gravida ii, in the last trimester of pregnancy. Special test meals of carbohydrate, fat, and protein were used together with a barium-water mixture (3 ounces barium, 8 ounces water), as a tracer, for the purpose of determining gastric motility by serial x-rays of the stomach. The carbohydrate meal consisted of 8 ounces of mixed fruit juice containing 17 grams of carbohydrate. The fatty meal consisted of 8 ounces of chicken broth containing 5 grams of fat. The protein meal consisted of 4 ounces of gelatin containing 8 grams of protein.

Every patient was submitted to a series of three x-ray studies, each study necessitating from one to five x-ray plates. In Study No. 1, each patient received one of the above-mentioned test meals with barium, in the last trimester of pregnancy. In Study No. 2, the same test meal with barium was repeated in a few days, this time with the addition of sedation, (Demerol 100 mg., scopol-

*Presented at a meeting of the Philadelphia Obstetrical Society, May 5, 1949.

amine 1/150 grain). In Study No. 3, the test meal with barium and sedation was given when the patient was in active labor. All patients studied had received nothing by mouth for a period of ten hours prior to these tests. In each study, an upright x-ray film of the stomach was taken three hours after the ingestion of the meal. If there was evidence of more than 10 per cent gastric retention at this time, subsequent films were taken at two-hour intervals.

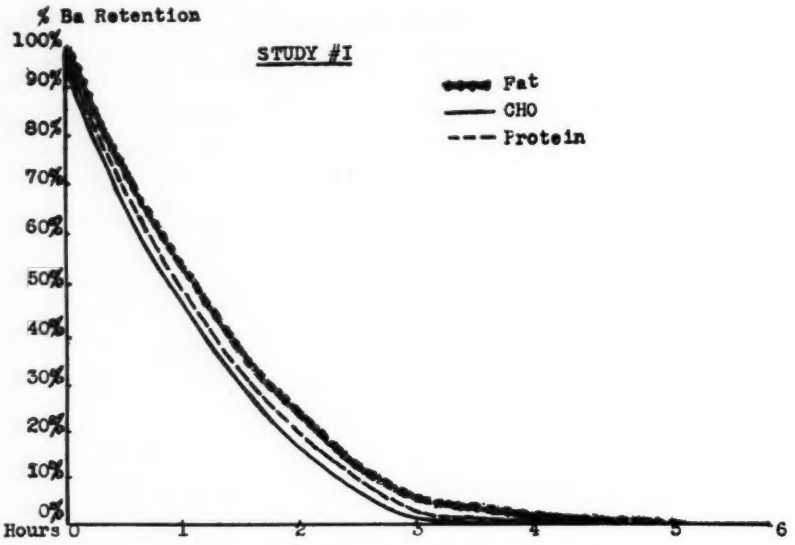


Fig. 1.—A graphic representation of the findings in Study No. 1. Regardless of the type of food ingested, all patients had almost complete gastric evacuation by the end of the three-hour period, and complete emptying at the end of the five-hour period.

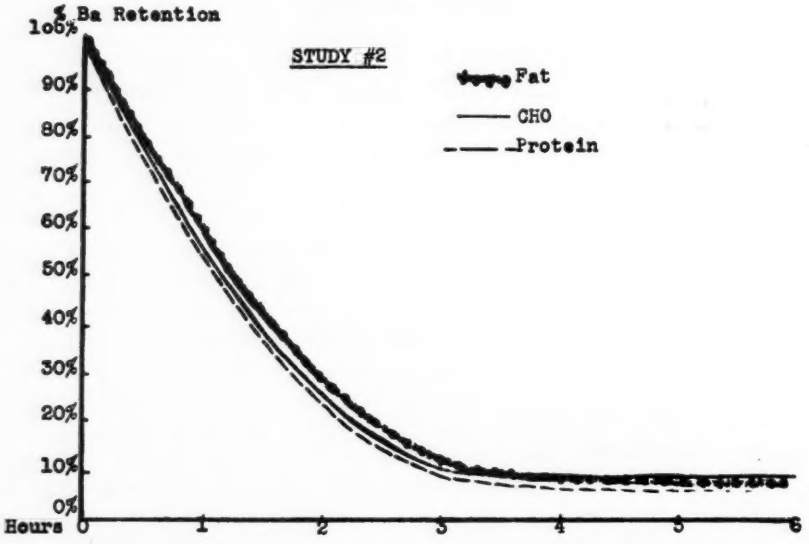


Fig. 2.—A graphic representation of the findings in Study No. 2. The addition of sedation was the only variable factor. This shows that an average dosage of sedation in labor retards gastric motility.

Of the original seventy-five patients selected for this study, only forty-two could be followed completely. Several factors were responsible for this. A few patients were admitted too close to the time of delivery to allow the

third study to be done. Others were unable to retain the test meal while in labor. Some patients did not adhere strictly to the fasting period which these studies demanded, and had to be excluded. Three patients required delivery by cesarean section.

All patients were delivered under spinal anesthesia or local pudendal block. Oral feedings were withheld, except for the test meal, and intravenous fluids substituted in labor.

The percentage of gastric retention was determined by the amount of barium present, as well as by evidence of a fluid level in the stomach. The results were estimated by our chief radiologist, Dr. Russell F. Miller.

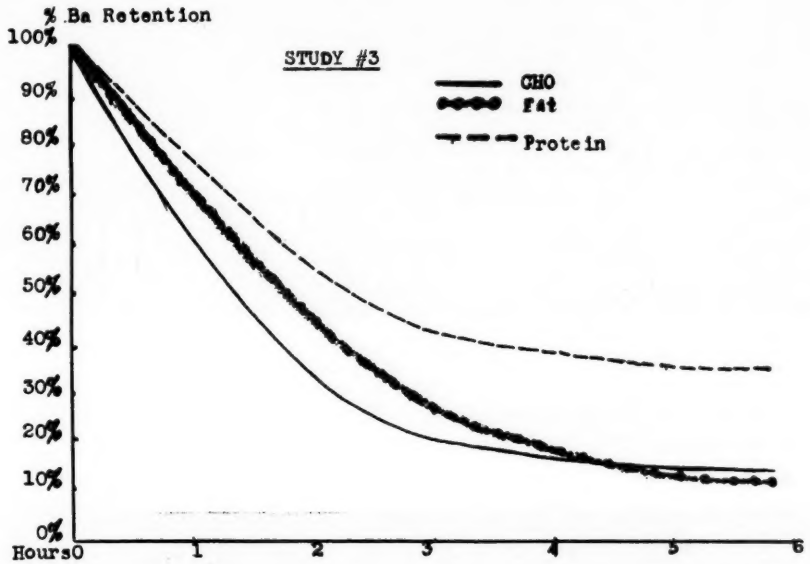


Fig. 3.—A graphic representation of findings in Study No. 3. Here both labor and sedation contributed to a marked delay in gastric emptying time. Two patients were followed up to the eleven-hour period after ingestion of the test meal, and were still found to have at least 10 per cent barium retention at that time.

Results

Table I shows the percentage of gastric barium retention three hours and five hours after the ingestion of each of the three test meals (Figs. 1 to 6).

TABLE I

	PERCENTAGE OF GASTRIC BARIUM RETENTION	
	3 HOURS	5 HOURS
Study No. 1 (Patient in Last Trimester of Pregnancy).—		
a. Patients receiving carbohydrate meal with barium	1.5	0
b. Patients receiving protein meal with barium	2.8	0
c. Patients receiving fatty meal with barium	5.0	0
Study No. 2 (Patient in Last Trimester With Sedation, Demerol 100 Mg., Scopolamine 1/150 Grain).—		
a. Patients receiving carbohydrate meal with barium	10.9	8.6
b. Patients receiving protein meal with barium	10.0	6.0
c. Patients receiving fatty meal with barium	11.6	7.7
Study No. 3 (Patient in Labor With Sedation, Demerol 100-Mg., Scopolamine 1/150 Grain).—		
a. Patients receiving carbohydrate meal with barium	20.3	12.5
b. Patients receiving protein meal with barium	43.2	37.0
c. Patients receiving fatty meal with barium	25.5	12.0

The presence of a fluid level in the cardiac end of the stomach is a most important feature in the determination of gastric retention. The barium, which is heavier than the food ingested, gravitates to the bottom of the stomach, while the supernatant fluid remains above it. This is analogous to the settling of barium in a barium-water mixture in vitro. When a fluid level was found in the cardiac end of the stomach, it was estimated that the stomach was approximately 75 to 85 per cent full. A fluid level in the fundal portion of the stomach indicated that there was 60 to 70 per cent retention.

TABLE II

	PERCENTAGE OF CASES SHOWING FLUID LEVEL	
	3 HOURS	5 HOURS
Study No. 1 (Patient in Last Trimester of Pregnancy).—		
a. Patients receiving carbohydrate meal with barium	0	0
b. Patients receiving protein meal with barium	0	0
c. Patients receiving fatty meal with barium	0	0
Study No. 2 (Patient in Last Trimester With Sedation, Demerol 100 Mg., Scopolamine 1/150 Grain).—		
a. Patients receiving carbohydrate meal with barium	17	17
b. Patients receiving protein meal with barium	40	40
c. Patients receiving fatty meal with barium	46	46
Study No. 3 (Patient in Labor With Sedation, Demerol 100 Mg. Scopolamine 1/150 Grain).—		
a. Patients receiving carbohydrate meal with barium	72	72
b. Patients receiving protein meal with barium	54	54
c. Patients receiving fatty meal with barium	69	69

Table II shows the percentage of cases with a fluid level in the cardiac end of the stomach three and five hours after the ingestion of the test meal (Figs. 4, 5, 6).

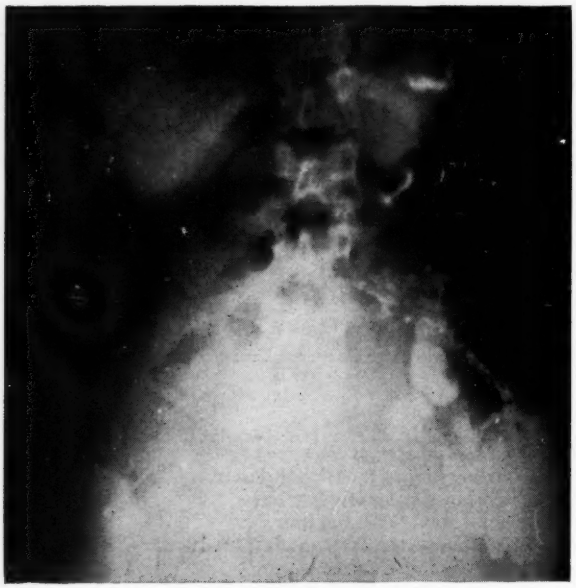
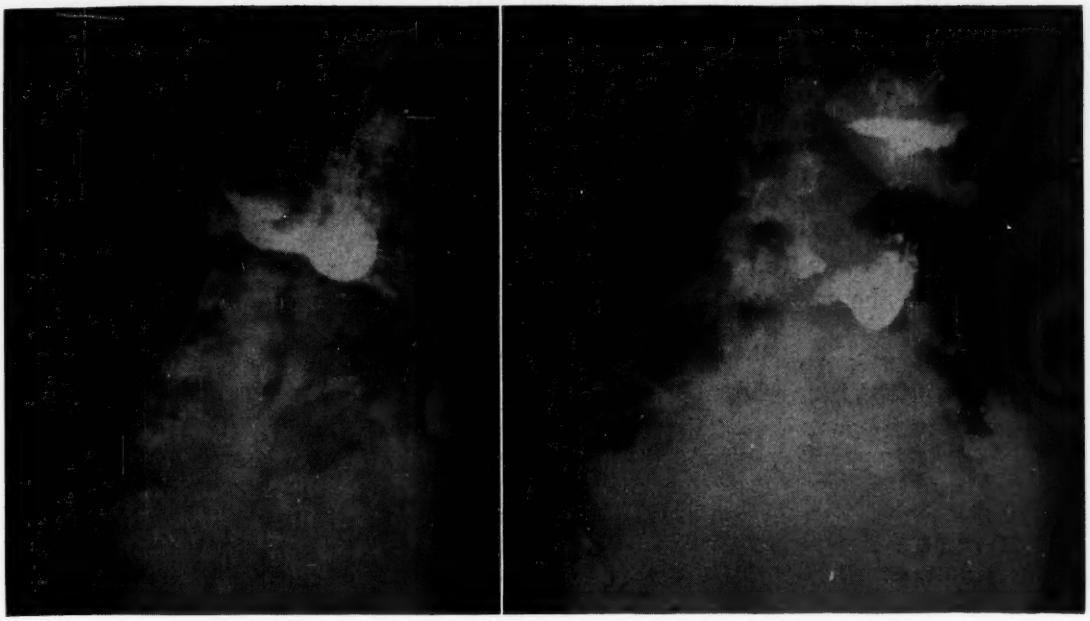


Fig. 4.—Study No. 1. At the end of the three-hour period, there is only a trace of barium in the stomach (1 to 2 per cent). The remaining barium lies within the jejunum along the left lateral and superior margin of the fundus of the uterus.

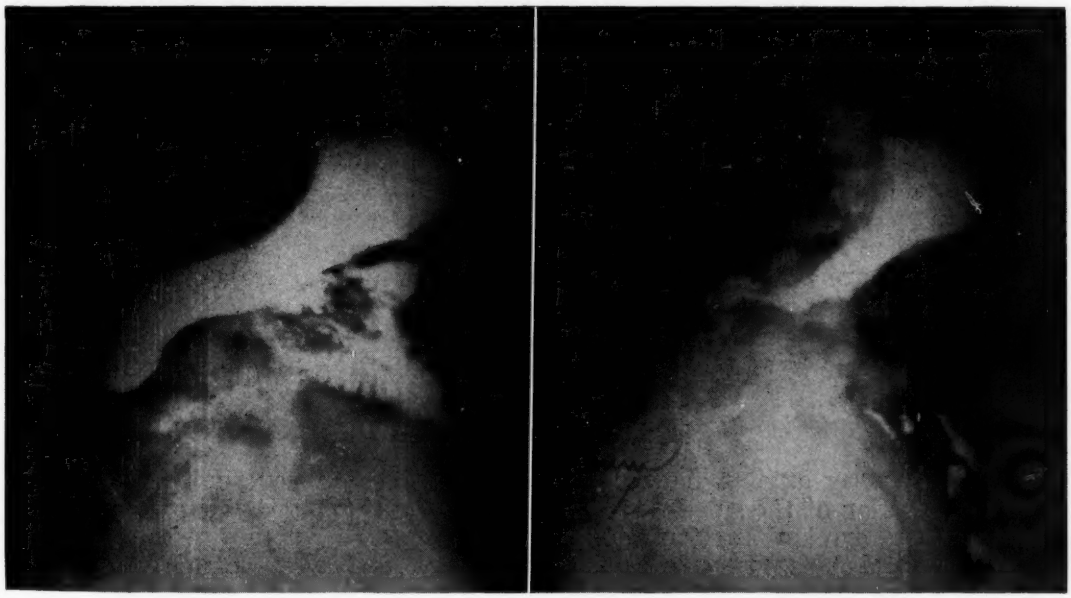
From Figs. 1 to 6, we can conclude that:

1. Pregnancy alone has little or no effect on the emptying time of the stomach.



A. *B.*

Fig. 5.—Study No. 2. *A*, at the end of the three-hour period, there is a moderate amount of gastric retention, approximately 15 per cent. Some of the barium is retained in the cardiac end of the stomach. *B*, Re-examination at the end of five hours still shows approximately 10 per cent barium retention.



A. *B.*

Fig. 6.—Study No. 3. *A*, There is a large amount of gastric retention at the end of the three-hour period. We would estimate this to be at least 65 to 70 per cent, with a supernatant fluid level in the cardiac end of the stomach. *B*, At the end of the five-hour period, there is still a gastric barium retention of 30 to 35 per cent, and a fluid level in the cardiac end of the stomach.

2. Sedation (Demerol 100 mg., and scopolamine 1/150 grain) decreases gastric motility. There is a gastric barium retention of 10 to 11 per cent at the end of three hours, and a retention of 6 to 8 per cent at the end of five hours after ingestion of test meals.

3. In labor with sedation as above, there is a more marked delay in the motility of the stomach, than with sedation alone, showing that labor is definitely a factor. There is a gastric barium retention of 20 to 43 per cent at the end of three hours, and retention of 12 to 37 per cent at the end of five hours after the ingestion of test meals.

4. In 54 to 72 per cent of all patients in labor with sedation, a fluid level is found in the cardiac end of the stomach from five to eleven hours after the ingestion of the test meal, indicating gastric retention.

5. There is a delay in gastric emptying time in labor with sedation, regardless of the type of food ingested.

Delay in gastric motility during labor can be explained on the basis of several factors. First of all, the analgesic combinations in dosages commonly used in obstetrics are factors which aid in the delay of passage of food from the stomach. Second, as Lull and Hingson[8] point out, the pyloric sphincter has a sluggish reaction time in labor, and may not relax at all when the patient is in pain or emotionally upset. Also, fear and apprehension prolong gastric emptying time.

There are conditions which favor aspiration of stomach contents in obstetrical anesthesia other than a delay in gastric motility. These include such things as regurgitation of small amounts of food when the uterus contracts, so as to compress the stomach, the abolition of the cough reflex during anesthesia, and the anesthetic agent itself.

In the management of labor, adequate nutrition is essential to combat both physical exhaustion and acidosis. However, the greater the intake, the more likely the danger of aspiration of gastric contents during anesthesia, as shown particularly by the delay in gastric emptying time in labor. Moreover, many patients in labor complain of nausea, vomiting, and inability to take food. The result is usually that the degree of exhaustion is often underestimated and the incidence of acidosis is high. It would seem feasible to cope with these problems by withholding oral feedings and substituting intravenous fluids in parturient women who are to be delivered under general anesthesia. On the other hand, there would be no contraindication to oral feedings in women who are to be delivered by an anatomic approach such as spinal or local anesthesia.

We have not considered washing out the stomach prior to obstetrical anesthesia, because it is both troublesome and ineffective in completely emptying the stomach.

Incidental Observations

These x-ray studies showed that, in about 90 per cent of the cases, a greater portion of the small bowel was visualized on the left side of the pregnant uterus, emphasizing the dextro-rotation of the uterus in pregnancy. In one instance, the transverse colon was displaced up above the level of the stomach. In another case, where no vomiting had occurred at any time, the lower end of the esophagus was visualized with barium, supporting the observations made by Chase,[4] that regurgitation occurs when the uterus contracts. Finally, there was no increase in the incidence of postspinal headaches, despite the fact that several patients were required to stand erect for x-ray films shortly after delivery under spinal.

Conclusions

This study shows that there is a definite delay in gastric emptying time in sedated women in labor; that this favors vomiting during obstetrical anesthesia, and, on occasion, inhalation of this vomitus with subsequent morbidity or even death. It recommends that such complications be avoided by withholding oral feedings and substituting intravenous therapy in women in labor unless they are to be delivered under spinal or local anesthesia.

In this way, one serious preventable complication of delivery can be avoided.

The authors wish to express their appreciation to Dr. Russell F. Miller, Dr. Dorothy L. Ashton, and the staff of the X-ray Department of the Woman's Hospital for their valuable assistance.

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THE MECHANISM OF ENDOMETRIOTIC PAIN

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THE menstrual toxin described by Smith and Smith[1] and the sympathetic nervous and endocrine systems can be linked together to account for some of the diversified characteristics of endometriotic pain. One notes in endometriosis that:

1. Pregnancy is an efficient prophylactic against endometriosis.[2]
2. Pain frequently subsides during a normal pregnancy and reappears after a variable period of time after a normal pregnancy.[3]
3. More pain occurs with ovulatory menstruation than in anovulatory menstruation.[4]
4. Minimal pain can occur with extensive lesions and extensive pain with minimal lesions.[5]
5. Removal or radiation of both ovaries will relieve the symptoms and cause the lesions to subside.[6]
6. A simple hysterectomy will frequently relieve the symptoms.[6]
7. A presacral neurectomy gives relief in about 70 per cent of the cases.[7]
8. A periarterial ovarian neurectomy will frequently relieve the pain of ovarian endometriosis.[8]

The etiology of endometriosis is still unsolved but the hypotheses of Sampson,[9] Meyer,[10] Novak,[11] Halban,[12] and Meigs[13] are the most widely accepted. The cyclic irritative bombardment by menstrual toxin of those tissues with the potential of endometriotic metaplasis may be a factor in the histogenesis of endometriosis. Since no menstrual toxin is formed during a normal pregnancy,[1] those tissues with the potential of endometriosis are given a rest from the periodic irritation of this vascular poison. This may account for the relative infrequency of endometriosis in women of a high parity. The theory of celomic metaplasia into endometriosis which was first suggested by Meyer and supported by Novak and Meigs has its basis in the embryological fact that the Müllerian duct system and the epithelium covering the ovary and the pelvic peritoneum are all derived from the primitive celomic epithelium, with the Müllerian ducts being the anlage of the Fallopian tubes, the uterus, and the upper portion of the vagina. Under some endocrine (Novak) or inflammatory (Meyer[10]) stimulus, the epithelial covering of the ovaries and pelvic peritoneum undergoes metaplasia into ectopic endometrial implants. Meigs[13] theorized that cyclic hormonal stimulation, uninterrupted by pregnancy or lactation, was an important factor in causing celomic metaplasia into endometriosis, but Venning[14] has shown that there is actually a marked increase in ovarian hormone levels during a normal pregnancy.

The protective vasoconstrictor sympathetic response of an individual to a noxious stimulus is dependent upon:

1. The amount of menstrual toxin in the circulating blood.
2. The threshold of the pain nerve endings.
3. The sensitiveness of the cerebral cortex to the pain impression made in the thalamus.

Smith and Smith[1] have demonstrated the presence of a fibrinolytic toxic euglobulin in the circulating blood of menstruating patients. This vascular poison is absent during a normal pregnancy but does appear during labor and in toxemias of pregnancy. Their experiments showed this menstrual toxin to be identical with the injury factor or necrosin of Menkin[15] which he isolated from the pleural exudate of dogs into whose pleural cavities he had injected turpentine. The experiments of Selye,[16] Smith and Smith, and Menkin tend to strengthen the concept that cellular injury from any cause will liberate a vascular toxin, which, by stimulating the adrenotropic factor of the anterior pituitary gland, causes adrenal hypertrophy along with an increased sympathetico-adrenal discharge. Selye[16] ties cellular injury to the lymphatic and the sympathetic nervous systems. According to Selye, a noxious stimulus causes involution of lymphoid tissue and hypertrophy of the adrenal glands, and in doing so, liberates antibodies formed in the lymphocytes in the lymph glands and increases sympathetico-adrenal activity.

Adrenal hypertrophy following any noxious stimulus causes:

1. A generalized vasoconstriction to prevent blood loss through its increased secretion of epinephrine.
2. An increased blood volume to prevent and combat shock through its increased secretion of desoxycorticosterone-like hormone which preserves water and salt for the extracellular fluids.
3. An increase in glucogenesis to make energy freely available, through the increased secretion of corticosterone.
4. Increased muscle tone and bulk to improve the reflex muscle spasm to protect the patient, through the increased secretion of adrenal androgens.

The end organs for pain consist of free nerve endings which are present virtually throughout the entire body. Relatively few, of course, are present in the viscera since the viscera are protected from the outside world.[17] The cutaneous pain nerve endings respond to any type of stimulus, provided this stimulus is sufficiently intense. On the other hand, the pain nerve endings which subserve the deep tissues and viscera are usually insensitive to those stimuli which readily arouse pain sensation in the skin. Muscle, tendon, and fascia are especially susceptible, however, to pain stimulation by chemical agents and distention. Keiffer[18] has described modified Pacinian corpuscles which subserve distention impulses, in the vicinity of the cervix. Pain also appears when muscle contracts in the presence of a poor blood supply. Ischemic muscular contraction causes an accumulation in the tissues of a lacticlike product of muscle metabolism, called the "P" or pain factor of Lewis, which, when it reaches a certain concentration, stimulates the pain nerve endings in the muscle.[19] The concentration of this "P" factor depends on the amount of muscle activity and on

the amount of blood available to carry it away from the body tissues. The soreness of healthy muscle which appears several hours after extensive exercise is thought to be due to this mechanism.

Pain stimuli, whatever they are, have one property in common, namely, that they tell of threatened injury. The sensation of pain serves therefore as a protective measure, by giving the individual warning of the injurious nature of the stimulus. Read[20] defines pain as a mental interpretation of an injurious stimulus, which serves to protect the individual against harm through the medium of the sympathetic nervous system. White[21] thinks of the sympathetic nervous system as an emergency protective mechanism which is not functioning all the time, but which is ready to go into action to combat any variety of adverse circumstances, either in the surroundings or in the internal machinery. Some of the conditions which arouse sympathetic activity are pain, strong emotion, extremes of temperature, asphyxia, hemorrhage, strong muscular exercise, dehydration, and hypoglycemia.

Hardy, Wolff, and Goodell[22] have found the threshold of the pain nerve endings to be rather constant in the unprejudiced patient, with the reaction of the patient to the impression of pain being the variable factor. They also found that trauma and disease tend to lower the threshold to pain. Haman,[23] on the other hand, found the threshold of the pain nerve endings to be slightly lower in dysmenorrhea patients and in others who are preternaturally sensitive. This disparity, however slight, is often sufficient, in his opinion, to cause one individual to feel impulses of pain to which another person would be indifferent.

Head[24] states that "the mental state of a patient has a notoriously profound influence over pain originating in the pelvic viscera." The variability of response to pain is dependent upon the sensitivity of the cerebral cortex to the impression of pain made in the thalamus when the pain impulses reach the latter structure. The perceptivity of the cerebral cortex to pain may be aggravated or inhibited by other cortical activity, e.g., in combat or in games of intense excitement, the participant is often unaware of severe injury, while the apprehensive patient may suffer pain even before being touched.[25] Wolff and Goodell[22] have shown that the pain threshold can be raised approximately 30 per cent for long periods of time by placebos, by distraction, and by suggestion or hypnosis. The success or failure of an analgesic is markedly influenced by the confidence or lack of confidence the subject has in the efficacy of the drug.

The whole subject of pain arising in or referred from the viscera is still highly controversial. It is fairly well agreed now that we are dealing with two types of visceral pain, namely, true and referred visceral pain. The afferent pain fibers which subserve true visceral pain are relatively few in number. They have a rather high threshold to visceral distention and pressure, a threshold which can be lowered by toxins, chemicals, and ischemia. True visceral pain is usually diffuse, poorly localized, and often continuous, dull, and boring. On the other hand, the locale of the well-localized referred visceral pain and muscle spasm depends on the innervation of the cutaneous (dermatome) and muscular (myotome) areas by the nerve roots of a corresponding spinal segment into which the afferent visceral fibers enter the spinal cord.

Mackensie[26] believed that these afferent visceral fibers were located in the autonomic nerves supplying the viscera, while Morley[27] believed the afferent visceral fibers to be located in the somatic nerves of the mesentery and parietal

peritoneum. Pollack and Davis[28] felt that the visceral afferent impulses induced reflex actions on the blood vessels in certain well-defined dermatome and myotome areas, and there, through some vasomotor, chemical, or hormonal process, stimulated the pain nerve endings in these tissues, sending pain impulses to the spinal cord. Whatever the mode of transmission of pain impulses to the spinal cord may be, it is generally agreed that these impulses ascend along the lateral spinothalamic tract to the thalamus where the impression of pain is made. This impression of pain is then transmitted to the cerbral cortex for evaluation and motor response to the dermatome and myotome areas. Head[29] has mapped out the segmental distribution of the cutaneous nerves to which pain is referred in disease of the various viscera. The referred muscle spasm combined with the impaired blood supply (adrenosympathetic vasoconstriction) causes more pain than the original source of the pain, and this pain caused by the muscle spasm may last twelve to twenty-four hours after the source of the referred visceral pain has been removed.[30]

The protective, vasoconstrictor, sympathetic response of an individual to a noxious stimulus is also dependent upon the activity of the ovaries and thyroid glands. Large doses of estrogens act as vasodilators by:

1. Being cholinergic, liberating the vasodilator, parasympathetic acetylcholine.[31]

2. Depressing the adrenotropic factor of the anterior pituitary gland, causing a decrease in vasoconstrictor activity.[32]

Progesterone acts as a vasoconstrictor, by tending to nullify the action of the estrogens. The action of the thyroid gland on the sympatheticadrenal system is not known, but Thompson[33] believes that thyroxin may inhibit the pituitary gland, so that in hypometabolism we may get an increased secretion of adrenotropic factor of the anterior pituitary gland along with an increased sympathetico-adrenal activity.

If one accepts the concept of pain as presented in this article as being sound, he can account for some of the characteristics of endometriotic pain which have puzzled us in the past.

Endometriotic pain usually subsides during normal pregnancy because of:

1. Improved circulation which is caused by:
   a. No menstrual toxin being formed during normal pregnancy.
   b. Marked increase in estrogen secretion as pregnancy progresses, with that of progesterone to a lesser degree.[14]

2. Decreased sensitiveness of the cerebral cortex. This may be attributed to the improved circulation of the cerebral cortex. A goodly percentage of parous women, after the first trimester of pregnancy, are emotionally more stable than the nonpregnant women. It is at the end of the first trimester of pregnancy that the estrogen blood levels first begin to become markedly increased, increasing the cerebral circulation.[14]

3. Absence of cyclic changes in the aberrant endometrial implants so that there is:
   a. No premenstrual distention of the ectopic endometrial implants to stimulate the pain nerve endings.
   b. No ruptured contents of the endometrial cysts to irritate the somatic pain fibers in the parietal peritoneum.

The duration of relief from endometriotic pain following parturition is dependent upon the locale of the ectopic endometriosis implants. Greater relief of a longer duration can be expected if the endometriosis is limited to the uterus, since the Keiffer corpuscles which subserve the distention impulses of the uterus are overstretched as the fetus passes through the cervix, with the result that there is an increased threshold to uterine distention.

Less pain occurs in anovulatory menstrual cycles than in ovulatory cycles because of:

1. Improved circulation which is caused by:
   a. Less menstrual toxin being formed during anovulatory menstruation.[1]
   b. Unopposed vasodilatation by the estrogens.
2. The low amplitude of muscular contractions of the uterus.
3. Decreased sensitiveness of the cerebral cortex, since premenstrual edema and ischemia occur only in the ovulatory menstrual cycles, causing an increased sensitiveness of the brain at that time.[35]

A minimal amount of endometriotic pain can occur with extensive lesions. This pain can be attributed to:

1. The possible slow growth of the endometriotic cysts, allowing the visceral pain nerve endings to adapt themselves to this gradual distention.
2. Congenital increased threshold of the free pain fibers.
3. Anovulatory cycles are more likely to occur with extensive lesions, which prevent the mechanical rupture of the mature Graafian follicles.

Extensive pain can occur with minimal lesions. This pain can be attributed to:

1. Congenital low threshold of the free pain fibers.
2. Ovulatory menstrual cycles are more likely to occur with minimal lesions than in those cases with extensive lesions, causing:
   a. Increased vasoconstriction due to:
      (1) Greater amount of menstrual toxin being formed.
      (2) More progesterone, which tends to nullify the vasodilatory action of estrogen.
   b. Increased cerebral cortex irritability due to premenstrual edema and ischemia of the brain.
   c. Increased amplitude of the uterine muscular contraction.[34]

A simple hysterectomy often can give considerable relief from endometriotic pain. This relief can be attributed to:

1. No menstrual toxin being formed once the uterus is removed.
2. Anovulatory ovarian cycles, which occur after the first ovulatory ovarian cycle following a hysterectomy.[36]
3. Removal of the uterus with adenomyosis. Adenomyosis is frequently present along with endometriosis,[37] causing:
   a. Premenstrual distention of the aberrant endometrial implants which may stimulate the free pain fibers in the muscle.
   b. Faulty myometrial contraction.
   c. Impaired myometrial circulation.
   d. Increased amount of circulating menstrual toxin due to the increased amount of menstruating endometrium.

A presacral neurectomy relieves around 70 per cent of the patients with endometriotic pain. This partial relief can be attributed to the following facts:

1. The presacral plexus does not innervate the ovaries and the parietal peritoneum which may have aberrant endometrial implants on them.[38]

2. The blood vessels have an inherent ability to maintain their tone following a sympathectomy.[39]
3. Denervated blood vessels still respond to sympathetico-adrenal impulses.[40]
4. Sympathetic nervous tissue has a definite tendency to regenerate.[41]

A periarterial ovarian neurectomy can give relief of endometriotic pain when the ectopic implants are limited to the ovaries, by resecting the vasoconstrictor efferent and the afferent pain fibers surrounding the ovarian arteries in the infundibulopelvic ligaments. Browne[38] did not observe any decreased fertility in those patients who had presacral and bilateral periarterial ovarian neurectomies done on them. The capacity for regeneration of the sensory pain fibers in the visceral nerve trunks is far less than that of the preganglionic visceromotor sympathetic fibers, and after their interruption no compensatory pain-conducting mechanisms come into play, with the result that permanent pain relief is certain.[42] Therapeutic measures designed to produce dilatation of the *entire* vascular bed do not seem rational for a disease state limited to a single part. The effect of any agent capable of producing maximal vasodilatation would be shocklike, and the original purpose of increasing the blood supply to the local part would be completely defeated. Hence attention should be concentrated on measures which produce local vasodilatation. Priscoline,[43] a sympatholytic drug, is believed to increase the vascularity of certain regions more than others, but to date there have been no control studies to show that it has a local adrenolytic effect on the genital organs. At the present time, the best of measures designed to cause a localized dilatation is sympathetic denervation of the affected part.[44]

Summary

A concept is presented whereby cyclic bombardment by menstrual toxin, uninterrupted by pregnancy, of those tissues with the potential of endometriotic metaplasia may be a factor in the histogenesis of endometriosis. The sympathetic nervous and endocrine systems are linked to the circulating menstrual toxin to account for some of the diversified characteristics of endometriosis.

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THE EFFECT OF VAGINAL pH ON WOUND HEALING

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THERE has been discussion in the literature in recent months concerning the effect of a sulfathiazole acid jelly on postoperative vaginal healing. Seigler[1] found that a sulfathiazole acid jelly controlled vaginal infections, thus accelerating healing, when used after plastic repairs, vaginal hysterectomies, and other vaginal surgery. It also controlled the discharge, odor, and other symptoms. It was, therefore, decided to determine the effect of the maintenance of a low vaginal pH alone on these postoperative vaginal incisions. By this means it could be shown whether the acid jelly was the principal factor in the accelerated wound healing noted, or the medication incorporated therein.

The acidity of the vagina has been shown to be a principal factor in maintenance of normal vaginal flora. Schroder's[2] classification of bacterial flora, correlated with the vaginal pH, is as follows:

TYPE	pH RANGE	pH AVERAGE	BACTERIA
I	3.92-6.85	4.7	Only gram-positive bacilli
II	4.25-7.62	5.57	Gram-positive bacilli plus other organisms
III	4.72-7.62	6.2	Organisms other than gram-positive bacilli. Cocci predominate

Thus it has been demonstrated that pH is important in a human vagina in which no operative procedure has taken place.

The acid pH in the vagina is due to the presence of lactic acid which is present as racemic lactic acid both in free and bound forms.[4] The lactic acid is produced by the vaginal mucosa and the concentration may reach as high as 2 to 3 per cent in the normal woman who is in the childbearing period. With the presence of a normal amount of lactic acid, a homogeneous flora of lactobacilli is found. The growth of other pathogenic bacteria is inhibited by the lactic acid and only relatively few of these are present.

The acidity of the vagina and the presence of lactobacilli vary, however, with different age groups. After the menopause, the vagina returns to a pH of neutral to 7.8, and the vaginal flora progresses toward the childhood type with a decreasing proportion of Döderlein's bacilli and an increasing proportion of other organisms.[4] Many of the patients who need vaginal repairs are postmenopausal. With these patients, an optimum condition for healing is not present even preoperatively. The present series of cases shows the following percentage of postmenopausal women:

AGE (YEARS)	NO. OF CASES	PER CENT	pH RANGE	NO. OF CASES DÖDERLEIN	PER CENT, CASES, DÖDERLEIN
35-39	8	33	4.0-6.0	7	87%
40-44	1	4	5.0	1	100%
45-49	3	12	4.0-7.0	2	66%
50-54	4	16.5	4.0-6.0	4	100%
55-59	1	4	6.0	0	0%
60-64	1	4	6.0	0	0%
65-69	5	20	5.5-6.5	4	80%
70-74	1	4	6.0	1	100%

It is interesting to note that, in this series of cases, some Döderlein bacilli were found even in the 70- to 74-year-old patients.

To determine the effect of vaginal acidity, three series of cases were run. The first group had only routine postoperative care. The second group had lactic-acid jelly instilled daily. The third group had a buffered acid jelly instilled in the vagina daily.

Jelly was used instead of local application, tampons, or douches, because it has been shown to have the following advantages[5]:

1. It is water dispersible so that it mixes easily with vaginal secretions.
2. Almost any type of medication can be incorporated in various concentrations.
3. The pH of the jelly is easily adjusted and evenly buffered to prevent alteration by vaginal secretions.
4. It spreads easily to cover the entire vaginal mucosa and yet it is retained for hours in the vaginal tract.
5. Postoperatively, with the use of the proper applicator, the jelly is easily introduced daily with a minimum of discomfort to the patient, and with a minimum of nursing time.

Procedure

Lactic acid jelly was used in one series. This was 4 per cent lactic acid in a water-soluble vaginal jelly. The pH of the jelly mixture was 2.0. No attempt at buffering was made. Aci-Jel, a commercial product with the following formula was introduced in another series:

FORMULA OF ACI-JEL*:

Acetic acid	0.92%
Oxyquinoline sulfate	0.025%
Ricinoleic acid	0.75%
Boric acid	3.00%
Glycerin	10.00%
pH	4.0

This preparation is buffered and has a pH of 4.0.

In both series, after any vaginal packing had been removed, 4 c.c. of the jelly were introduced by a vaginal applicator each morning postoperatively during the patient's hospital stay. This was done by the nurse and caused the patient, surprisingly enough, very little discomfort.

In each of the three series certain factors were checked daily or at regular intervals:

1. *Vaginal pH.*—This was taken daily at approximately 5:00 P.M. It was felt that if the jelly used was inserted into the vagina in the morning, the maintenance of a lowered pH could be determined by evening. The vaginal pH was determined by the use of hydrion papers. These had been previously checked

*Aci-Jel, Ortho Pharmaceutical Corporation, Raritan, N. J.

by an electric potentiometer. It is recognized that indicator papers are not as satisfactory as the use of the potentiometer or glass electrode. However, since indicator papers were used in all three series, the results should be comparative. The secretions were taken from the lower one-third of the vagina and were placed on the indicator paper. Readings were taken immediately.

2. *Vaginal Smears.*—Daily slides were made of the vaginal secretions in all three series. No cultures were taken. These slides were stained with Gram stain. They were then examined for the presence and type of bacteria. Döderlein's lactobacilli and Staphylococci were easily identified. Other organisms were listed only as gram-positive and gram-negative cocci, and gram-positive and gram-negative bacilli. The relative number of each type was checked so that a good Döderlein response could be recognized. Slides taken during the time that packing soaked in Zephiran was in the vagina showed only crenated red blood cells. No bacteria could be identified during this period.

3. *Catgut Condition.*—This was found to be a more important factor than had at first been supposed. There is a more rapid softening of catgut in the vagina than in other locations because of the constant presence of the vaginal discharge and the rapid postoperative growth of bacteria. If there is any superimposed infection over and above that normally present, the dissolution of the catgut takes place even more rapidly. Chromic catgut No. 1 was used in all the repairs in the series. The effect of the jelly on the catgut was determined by the relative softness or hardness of the catgut, the presence of sutures on the perineal pads, and the number of sutures remaining in place on day of discharge.

4. *Patient Comfort.*—This one factor alone seems to me to justify the use of or failure to use an acid jelly. Any doctor or nurse associated with patients who have had vaginal repairs would agree that a certain percentage of patients will complain daily of the odor of the profuse vaginal discharge and the discomfort of it on their perineal pads. The discharge is very irritating if perineal care is not given at frequent and regular intervals.

Another factor in patient comfort was pain or burning which might have been associated with the instillation of the acid jelly. After all, it was inserted with a vaginal applicator onto a fresh incision. However, if the acid jelly could relieve the odor of the vaginal discharge without too much discomfort on its instillation, the jelly would be well worth using.

Results

Table I shows the findings when no treatment was instituted except that used routinely postoperatively. The pH ranged from 4.0 to 10.0 postoperatively. The average pH range was 5 to 7. This is definitely in the alkaline range. It is, therefore, not surprising that Type II, Döderlein and other bacteria, and Type III, other bacteria only, were the only types of discharge present postoperatively. Döderlein bacilli appeared on the fifth day in five cases, on the seventh day in one case, and on the eighth day in four cases. In one case no Döderlein bacilli was seen either pre- or postoperatively. There were a large number of staphylococci and gram-negative bacilli present in all postoperative smears in this series. The catgut showed definite softening by the fifth day. By date of discharge about one-half the sutures were still present but easily removed by rubbing a gloved finger over the surface. Four patients out of ten complained of the odor and discomfort associated with the discharge.

Table II shows the findings when lactic-acid jelly was instilled daily. The pH taken eight hours after the jelly was used was no better maintained in the acid range than if no jelly had been inserted. In only one case was the pH range 3.5 to 5.5. In all the other cases the pH range was from 4 to 7, with four having a range of only 6 to 7. This would tend to show that an unbuffered solu-

tion does not maintain an acid pH over a long period of time. To check this, hourly pH readings were taken after lactic-acid jelly had been placed in the vagina. After instillation the pH was 4.5. For the next six hours it became steadily more alkaline until it again became stationary at a pH of 6.0. Döderlein bacilli appeared in all cases but one on the second day after the lactic-acid jelly had been used. Other bacteria were very rare in almost all of the slides contrasting sharply with the relatively dirty slides seen when no medication was used. In eight of the ten cases, the sutures were very hard even on the tenth postoperative day. There was relatively little induration of the suture line, and most of the sutures were still present on the day of discharge. In fact, one staff member questioned the wisdom of discharging a patient who had been receiving lactic-acid jelly. The sutures were so hard, and the line of incision showed so little induration that she feared adequate healing had not taken place. The patients had no odor to their discharge and they felt cleaner after the lactic-acid jelly had been instilled. However, five patients complained of burning for as long as one-half hour after the lactic-acid jelly had been used. There was only one patient who complained of pain when the applicator was introduced.

TABLE I

CASE	pH RANGE	SMEAR	SUTURES	COMFORT
A_1	5.5-7	Staphylococcus plus gram-negative bacilli	Catgut swollen	Foul smell
A_2	6.5-10.0	Döderlein present but rare after fifth day. Staphylococcus and gram-negative bacilli present	Catgut intact but soft	Odorous
A_3	5.0-7.5	Döderlein present. Fifth day Staphylococcus plus gram-negative bacilli	Sutures intact but soft	No complaints
A_4	6.0-7.5	Döderlein present occasionally on seventh day. Dirty slides with many bacteria	Some dissolved out	Foul smell
A_5	6-7	Döderlein present on eighth day. More present by tenth day	Intact but purulent discharge	No complaints
A_6	5-7	Döderlein present occasionally on eighth day but rare. Rare, preoperatively also	Soft, much discharge around	No complaints
A_7	5-7	Döderlein present on eighth day. Few present on fourth day	Catgut dissolved. No sutures remaining	Foul smell
A_8	6-7	Döderlein appeared on fifth day and continue to present	Catgut almost all disappeared	No complaints
A_9	4.0-7.0	Döderlein appeared on fifth day. pH on that day 7.0	All softened and easily removed	No complaints
A_{10}	4.0-6.1	Döderlein present fifth day. Decreasing number staphylococcus and *B. coli*	Soft, almost all dissolved out	No complaints

The third series shown in Table III used Aci-Jel, a buffered acid jelly, and included only six patients. The pH range with the use of this medication ranged from 4.0 to 7.0, five out of the six having a range from 4 to 6. This shows an excellent maintenance, using a buffered jelly, of a relatively neutral to acid vagina, compared with a pH of 5 to 7, with an extreme of 10.0 in the unmedicated controls. The Döderlein bacilli appeared from the second to fifth day, with only one having no lactobacilli until the eighth day. The other bacteria were definitely inhibited although not as markedly as in the lactic-acid series. The sutures showed some softening in three out of the series of six. However,

TABLE II. LACTIC ACID

CASE	pH RANGE	SMEAR	SUTURES	COMFORT
B_1	3.5-5.5	Excellent Döderlein response second day. Others depressed	Intact	White profuse watery discharge. No odor
B_2	4.0-7.0	Döderlein appeared early second day	Some still intact on thirteenth day	No complaints
B_3	6.5-7	Döderlein present after third day but rare after fifth day. Bacteria rare	Catgut intact	Burning on instillation. Comfort later
B_4	4-6	Cocci present. Döderlein not numerous but present after first postoperative day	Intact. Absolutely no softening	Burning when instilled
B_5	5-7	Döderlein present but rare after second postoperative day. Staphylococcus and Diplococcus predominate. Cocci	Some necrosis. Sutures came out hard and intact	Cleaner after instillation
B_6	6-7	Excellent Döderlein response after second postoperative day. Other bacteria rare	No induration suture line. No soft sutures	Slight pain when instilled
B_7	6-7	Good Döderlein response third postoperative day. Numerous Staphylococci	Sutures intact twelfth day	Burning
B_8	6-7	Numerous Döderlein after eighth day but present from second day on. Other bacteria rare	Intact	Feels better and cleaner
B_9	4-7	Staphylococcus and *B. coli*. Döderlein present on fifth day	No sutures left tenth day	Burning few minutes after each instillation
B_{10}	4-6	Good Döderlein response from second day until sixth day, then decreased. *B. coli* increased	Some still intact	No complaints

this softening was less marked than in the control series in which no jelly of any kind was used. Patient comfort was the most outstanding feature of this series. The patients noted no odor and they felt much cleaner after the Aci-Jel was

TABLE III. ACI-JEL

CASE	pH RANGE	SMEAR	SUTURES	COMFORT
C_1	6.0-7.0	Döderlein response third day. Bacteria depressed	Softened, one area separated	No discomfort
C_2	4.5-6.0	Döderlein appeared early fifth day. Preoperatively Staphylococcus infection. Staphylococci numerous postoperatively	Softened	No discomfort
C_3	4.0-6.0	Döderlein appeared eighth day. Numerous Staphylococci and *B. coli*	Slightly dissolved	Slight burning on insert of Aci-Jel
C_4	4.0-6.0	Excellent Döderlein response on second postoperative day. Bacteria inhibited	All in good condition	No discomfort
C_5	4.0-6.0	Excellent Döderlein response on second day. Other bacteria inhibited	All intact and hard	No discomfort
C_6	4.0-6.0		All intact	No discomfort

instilled. In only one case was there slight burning on instillation of the jelly. Two of the other patients asked if it could be used twice daily since they got so much symptomatic relief.

Conclusions

Three series of cases have been reviewed; a control series, a series using lactic-acid jelly instillations daily, and one series using Aci-Jel vaginal medication daily.

These were checked for pH maintenance, bacterial flora of the vaginal discharge, catgut condition, and patient comfort.

The lactic-acid jelly failed to maintain an acid vagina. It did, however, produce an excellent Döderlein response, and inhibited the pathogenic flora. The catgut stayed in excellent condition in this group, better than in the control or Aci-Jel series. Patients were more comfortable than in the control series, but several complained of burning after instillation of the medication.

The Aci-Jel series had the best maintenance of vaginal acidity, probably due to the buffering of the jelly. There was a good Döderlein response. Sutures were not in as good condition as with the lactic-acid jelly, but were maintained better than in the control series. Patient comfort was outstanding with complete symptomatic relief.

A buffered acid jelly would seem advantageous postoperatively in vaginal plastic operations.

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A COMPARATIVE STUDY OF INTRATHECAL EPHEDRINE SULFATE, INTRATHECAL PONTOCAINE, AND INHALATION ANESTHESIA FOR OBSTETRICAL DELIVERY

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WHILE spinal anesthesia has certain advantages over inhalation types for obstetrical delivery, the relatively high incidence of complications associated with its administration limits its value. All the agents currently in use are potentially dangerous to the gravid woman and her infant even when administered under ideal conditions. If these disadvantages can be reduced to a minimum and if relief from pain can be obtained without increasing maternal or fetal risk, spinal anesthesia in obstetrics will be of greater value. It was with this thought in mind that an attempt was made to obtain anesthesia sufficient for delivery by the intrathecal injection of ephedrine sulfate in the seventy-five patients reported here.

This investigation was prompted by the work of Ruben, Kamsler, and Howell,[1] who reported its successful use in the relief of pain associated with surgery of the lower extremities. Schultz[2] first produced local anesthesia lasting five to eighteen minutes in the skin of the forearm in a human being with 0.1 per cent ephedrine hydrochloride in 0.73 per cent saline solution. He also achieved complete motor and sensory anesthesia of eighty to one hundred forty-nine minutes duration by the intraspinal injection in frogs of 0.1 mg. of ephedrine hydrochloride per gram of body weight. No neurological sequelae were observed. It was also noted that the application of a 5 per cent solution of the same drug directly to the exposed sciatic nerve blocked impulses to the gastrocnemius muscle. In 1946, Potter and Whitacre,[3] who reported on 2,500 cases of spinal anesthesia produced with Pontocaine, ephedrine, and dextrose, concluded that "ephedrine potentiates the action of Pontocaine, decreases the dosage, and has no apparent deleterious effects." They were unable to demonstrate anesthetic properties when ephedrine-dextrose solution was given alone.

Chemical and Pharmacological Properties.—Chemically ephedrine is an aliphatic amine obtained from various plants belonging to the same genus, ephedra, which are indigenous to the temperate and subtropical latitudes of Europe, Asia, and America. The Chinese have used ephedrine in form of ma huang to produce diaphoresis, reduce fevers, and as a mydriatic agent for over 5,000 years. The active principle was first isolated from ma huang by Yamanashi in 1885, and Nagai, who named it ephedrine, obtained the alkaloid in pure form two years later. A study of the pharmacological properties and actions of ephedrine was reported by Chen and Schmidt[4] in 1924. The administration of ephedrine is followed by stimulation of the heart muscle and a rise in blood pressure associated with constriction of the arterioles, relaxation of the smooth muscle of the bronchi and gastrointestinal tract, dilatation of the pupil, an increase in the metabolic rate, and stimulation of the central nervous system. The fate of ephedrine in the body is unknown.

Method

Ephedrine sulfate was administered to seventy-five selected normal patients in an attempt to produce anesthesia sufficient for delivery and was given to the primigravidas after perineal bulging had been noted and to the multiparas when the cervix was almost completely dilated. The injection was carried out according to the following technique: With the patient in the lateral position on the delivery table and the skin properly prepared and the patient draped, a spinal puncture was made with a 20 gauge needle in the fourth lumbar interspace and when a free flow of spinal fluid was obtained the anesthetic mixture was injected slowly between uterine contractions. In this series 2 ml. of a hyperbaric solution containing 1 ml. (50 mg.) of crystalline ephedrine sulfate solution without preservative and 1 ml. of 10 per cent dextrose solution were used. Following the injection the patient was placed in the dorsal position without a pillow for a period of thirty to sixty seconds, after which the table was elevated fifteen degrees to aid in the low fixation of the anesthetic agent. The maternal pulse rate, blood pressure, and fetal heart sounds were taken and recorded at one-minute intervals until the completion of the delivery.

In order to evaluate the results more accurately, the charts of 500 unselected patients recently delivered under spinal anesthesia and 100 unselected patients delivered with the aid of inhalation anesthesia were reviewed and compared.

TABLE I. RESULTS

	EPHEDRINE	PONTOCAINE	INHALATION
Primigravidas	28	296	22
Para i, plus	47	204	78
Dose	50 mg.	2.5-6 mg.	
Levels above T-10	8 (10.6%)	30 (6%)	
Length of anesthesia	60-90 minutes	90 minutes	
Failures	20 (27%)	35 (7%)	
Sedation before delivery	41 (54.6%)	396 (79.2%)	49 (49%)

With ephedrine, sensory anesthetic levels as determined by skin prick reached T-10 to 11 in the average patient: the highest level noted was to T-7. The maximum time over which these levels were maintained was ninety minutes. Pelvic anesthesia adequate for delivery was obtained in 73 per cent of the seventy-five cases studied. Uterine activity was not disturbed, as evidenced by the fact that there was noted neither an alteration in duration of and interval between uterine contractions nor an increase in postpartum bleeding, the estimated blood loss being less than 200 c.c. Anal sphincter and pelvic muscle relaxation was noted but was less than the complete paralysis observed after Pontocaine administration. With Pontocaine, anesthetic levels to T-10 were obtained in the average case, the highest level observed being to T-5. Anesthetic levels sufficient to relieve pain from uterine contractions were maintained for ninety minutes, but pelvic anesthesia lasted for three to four hours. Anesthesia satisfactory for delivery was obtained in 93 per cent of the 500 cases observed. Uterine contractions as evaluated by palpation were slightly intensified for approximately five minutes after the injection; thereafter the preinjection pattern was resumed. Postpartum uterine tonus was normal as evidenced by an average estimated blood loss of less than 250 c.c.

Maternal Complications

In the experimental series the following complications which may be attributed to the ephedrine sulfate were observed:

1. Nausea and vomiting beginning from five to ten minutes after the injection in eleven cases. In two it began with a drop in blood pressure and disappeared promptly when the pressure stabilized.

2. Profuse generalized diaphoresis in four cases.

3. Tachycardia, as evidenced by an increase of at least twenty beats in the pulse rate, was encountered sixteen times, 21 per cent. The highest rate was 160, and the average 140. The only factor other than the ephedrine which might have been responsible for the increased pulse rate was scopolamine which had been given with Demerol to nine of these patients for analgesia during labor. In thirteen others, however, receiving the same medication no increase in pulse rate was noted.

TABLE II. TYPES OF DELIVERIES

	EPHEDRINE	PONTOCAINE	INHALATION
Breech	2	7	6
Spontaneous	22	65	59
Outlet forceps	36	251	23
Low forceps	15	159	10
Midforceps	0	18	2
Rotations	2	0	0

In both groups significant alterations in blood pressure (20/15 mm. Hg), if present, were usually noted three to five minutes after the injection. In all such patients oxygen was administered to protect the fetus from anoxemia. In the ephedrine series two transient decreases in the pressure were observed with sensory anesthetic levels to T-7. The two pressure elevations noted in the ephedrine series were maintained for fifteen minutes to two hours, and in one instance in a sensitive patient the pressure reached a level of 200/90 mm. Hg. In five of the seventy-six patients whose blood pressures were depressed following Pontocaine, intravenous glucose was started in addition to the oxygen. Only two minor elevations were noted in the Pontocaine series. As observed from Table III, there was only one pressure change in the inhalation series. This was not due to blood loss since the decrease was first noted during the induction of the anesthetic.

TABLE III. MATERNAL COMPLICATIONS

	EPHEDRINE	PONTOCAINE	INHALATION
Blood pressure changes	9 (12%)	78 (15.6%)	1
Elevations	2 (2.6%)	2 (0.4%)	0
Decreases, systolic	7 (9.3%)	76 (15.2%)	1
20-30 mm. Hg	1	19	–
30-40 mm. Hg	3	32	–
40 plus	3	25	1
Pulse changes	18 (24%)	21 (4.2%)	
Elevations	16* (21%)	11* (2.2%)	
Decreases	2† (2.6%)	10‡ (2.0%)	

*Highest, 160.
†Lowest, 88.
‡Lowest, 68.

Fetal physiology is disturbed to varying degrees depending upon the anesthetic agent (Table IV). Alterations in the fetal heart rate of thirty beats per minute or more occurring between the time of injection and delivery were considered significant. In the ephedrine series it was thought that the severe alterations in the fetal heart rate were due to pressure exerted upon the fetal head from the perineum because in all cases except one respirations were initiated spontaneously and immediately after delivery. One infant was depressed and required resuscitation. This explanation, however, is not tenable in the Ponto-

caine series because eleven of the fetuses that had alterations in the fetal heart rate were also depressed after delivery and required resuscitation. It is possible that this may be an effect of reduced blood flow through the uterus due to the increase in tonus immediately following the administration of the drugs as noted in the foregoing.

TABLE IV. FETAL PHYSIOLOGY

	EPHEDRINE	PONTOCAINE	INHALATION
Alteration in fetal heart rate	7 (9.3%)	80 (16%)	1 (1%)
Increase	2	34	1
Decrease	5	46	0
Respiratory depression	1 (1.3%)	41 (8.2%)	13 (13%)

Of the forty-one fetuses that were depressed after delivery with Pontocaine, fifteen were delivered from patients who had sedation less than two hours before delivery: one was delivered from a mother who had received 5 mg. and who had a drop in systolic blood pressure from 120 to 90 and a decrease in fetal heat rate from 140 to 108; three were delivered by midforceps extraction; six from patients who had significant drops in blood pressure with levels below T-10; and two from mothers who had anesthetic levels above T-7 and in whom the systolic blood pressure fell more than 30 mm. Hg.

With inhalation anesthesia thirteen of the infants were depressed. Five of these infants were delivered from patients who had received deep ether anesthesia for operative deliveries and two from patients who had been sedated within the hour before delivery. In the remaining six infants it does not seem likely that the anesthetic agent was responsible. All deliveries were spontaneous, nitrous oxide and oxygen being administered only in an amount sufficient to reduce the terminal pains of delivery.

There were no fetal deaths in this series which could be attributed to the anesthetic agent involved.

As noted from Table V, headache was a constant and persistent postpartum complication of the intrathecal anesthetic agents. It usually appeared on the second or third day and could not be correlated with dosage of an anesthetic agent, position in bed post partum, or with the degree of ambulation. Its response to any form of therapy was uniformly poor. An interesting observation in the Pontocaine series is that the incidence of headache was twice as great in private as in ward patients. It is difficult to evaluate this difference since in the former group minor symptoms may be exaggerated by both patient and physician.

TABLE V. POSTPARTUM COMPLICATIONS

	EPHEDRINE	PONTOCAINE	INHALATION
Headache	8 (10%)	67 (13.4%)	0
Ward	8	138 11 (7.9%)	
Private	0	362 56 (15.4%)	
Catheterization	5 (7%)	33 (6.6%)	5 (5%)
Repeat catheterization	0	9	0

The incidence of catheterization for urinary retention because of bladder atonicity was uniform with all of the anesthetic agents, but repeat catheterization was more frequently required after Pontocaine.

The average estimated blood loss with all forms of anesthesia was in the range of 200 to 250 c.c., but the incidence of postpartum hemorrhage varies considerably depending upon the anesthetic agent used. With ephedrine there were

no cases of postpartum hemorrhage, whereas with Pontocaine the incidence was 4.2 per cent and with inhalation anesthesia 10 per cent; however, the patients in the ephedrine series were all carefully selected normal cases. The increased incidence of postpartum hemorrhage with inhalation anesthesia is understandable because in ten cases deep surgical anesthesia was induced for operative obstetric deliveries. In these instances in which the uteri were purposely relaxed, there was excessive uterine bleeding until muscle tone had recovered. The greatest loss was estimated to be approximately 1,500 c.c. of blood following the decomposition and extraction of a frank breech in a primipara.

TABLE VI. BLOOD LOSS AND HEMORRHAGE

	EPHEDRINE	PONTOCAINE	INHALATION
Average estimated blood loss	200 c.c.	250 c.c.	200 c.c.
Postpartum hemorrhage (No. of patients)	0	21 (4.2%)	10 (10%)

Summary

In a group of carefully selected patients without complications intrathecally administered ephedrine sulfate solution produced anesthesia satisfactory for delivery in 73 per cent of seventy-five patients. An analysis of this series and a comparison with the results when other agents were used reveal that there is no appreciable decrease in the incidence of maternal or fetal complications. In view of this and the high percentage of failures it is felt that intraspinal ephedrine sulfate solution is of little value for frequent use as an anesthetic agent in obstetrics. However, the results obtained justify continued investigation in an attempt to learn more about its mechanism of action and to determine its range of usefulness in the production of anesthesia.

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3401 NORTH BROAD STREET

LIVER FUNCTION DURING PREGNANCY AND THE PUERPERIUM, AS MEASURED BY THE CEPHALIN-CHOLESTEROL FLOCCULATION, THE THYMOL TURBIDITY, AND THE BROMSULFALEIN TESTS*

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MANY different tests have been employed to evaluate liver function during pregnancy and the complications of pregnancy. Yet, at the time this work was started, there were no data available in the literature on the cephalin-cholesterol flocculation test in the normal or complicated pregnancy or on the thymol turbidity test in the late toxemias of pregnancy, though Maclagan[1] has reported the thymol turbidity test negative in twelve cases of undesignated pregnancy. We have, therefore, determined the value of the thymol turbidity and the cephalin-cholesterol flocculation tests together with the bromsulfalein test in pregnancy and in the late toxemias of pregnancy. These tests seem to be, as judged by the current literature dealing with this subject,[2-8] the most sensitive tests now available for the evaluation of liver function.

Subjects and Methods

Simultaneous cephalin-cholesterol flocculation, thymol turbidity, and bromsulfalein tests were carried out on sixty-eight women taken from both the outpatient and inpatient services of the Woman's Clinic of the New York Hospital. Twenty-seven of these were essentially normal antepartum patients‡ from 7 to 42 weeks pregnant, distributed evenly. Ten were normal postpartum patients. Twenty-two were either ante- or postpartum patients in whom the course was complicated by hypertension. Nine were normal nonpregnant women of childbearing age, both pre- and postoperative from the gynecological service. Of the twenty-two patients with hypertension, four are classified as eclamptics, eight as severe pre-eclamptics, one of whom subsequently developed intrapartum eclampsia, nine as mild pre-eclamptics, and two as hypertensives. The severe pre-eclamptic who developed eclampsia was tested three different times, thus a total of seventy tests are recorded in the data for the cephalin-cholesterol flocculation and thymol turbidity tests and sixty-five for the bromsulfalein test (three normals were lost) plus the twelve used only in the dosage determination described below.

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‡Those not absolutely normal were all less than 20 weeks pregnant and included three patients with threatened abortion (0, 5.4, and 5.6 per cent retention of bromsulfalein); 3 patients admitted for vomiting of pregnancy (0, 2.3, and 2.5 per cent retention of bromsulfalein) and 1 psychopath (6.3 per cent retention of bromsulfalein). The thymol turbidity and the cholesterol flocculation tests were all normal.

The blood specimens for the cephalin-cholesterol flocculation tests and the thymol turbidity tests were drawn, in so far as possible, from the fasting patient, following which the measured dose of bromsulfalein was injected through the same needle. The specimen for the determination of bromsulfalein was withdrawn from the opposite arm forty-five minutes after the dye was administered, as recommended by Mateer and associates.[5]

The Hanger cephalin-cholesterol flocculation test[9] was performed as modified by Frisch and Quilligan.[10]

The thymol turbidity test was performed as described by Maclagan[11] the turbidities being determined with the Klett-Summerson photometer using filter 42.[12]

The concentration of the bromsulfalein in the serum was determined with a Klett-Summerson photometer using filter 54.

At one point in this survey it seemed that the bromsulfalein dosage should be calculated on the basis of the nonpregnant weight of the patient since the bromsulfalein does not seem to enter the fetal circulation.[13, 14] On the basis of this assumption the patients with complicated pregnancies were nearly all given bromsulfalein as a function of their weights at the time they became pregnant, while most of the controls were given the dye as a function of their actual weights. A re-evaluation of this particular point revealed that five pregnant women (34 to 41 weeks pregnant) given the dye as a function of their pregnant weights retained an average of 3.8 per cent of the administered dye (range 3.1-4.7) while seven (32 to 38 weeks pregnant) given the dye as a function of their nonpregnant weights retained an average of 3.7 per cent of the dye (range 0.0 to 6.1). It does not seem, therefore, too important which weight is used to calculate the bromsulfalein dosage.

These methods are those in use at the Central Chemical Laboratories of the New York Hospital[15] and were chosen for that reason so that these data might be compared with any other data accumulated here along these lines.

Results

The values considered to be normal for the cephalin-cholesterol flocculation, the thymol turbidity, and the bromsulfalein tests by the Central Chemical Laboratories of the New York Hospital are 0 to 6 plus (values from 6 to 10 plus are considered questionable) for the cephalin-cholesterol flocculation test; 0 to 4 units of turbidity for thymol turbidity; and 4 per cent or less retention after forty-five minutes for bromsulfalein. These values have been arrived at by actual survey and are not arbitrary.[15] Since the results obtained in this study on a limited number of normal patients are in accord with these values it seems justifiable to discuss the data in terms of these limits.

The cephalin-cholesterol flocculation and the thymol turbidity tests yielded results which are within normal limits during normal pregnancy, the early puerperium, eclampsia, and pre-eclampsia with but two exceptions. In one of these, a mild pre-eclamptic, the thymol turbidity test was 7 at 37 weeks with normal values for the cephalin-cholesterol flocculation and bromsulfalein tests. The other was an intrapartum eclamptic at term who was hospitalized in the twenty-ninth week of her pregnancy with severe pre-eclampsia. This patient's cephalin-cholesterol flocculation test was 0 at 32 weeks; 10 during the first day, 18 on the forty-second, and 0 on the seventy-fifth day post partum. Her thymol turbidity test was normal at these times except for the forty-second day post partum when it was 6. Her bromsulfalein test showed 7.8 per cent retention at 32 weeks; and 8.9 per cent retention on the first post partum day. It was not determined thereafter. Unfortunately, the one high cephalin-cholesterol floccu-

lation value (the 18) is highly suspect as an artifact so too much significance is not attached to this particular observation. No other data, clinical or other, are available to indicate why these two cases should differ from the others, or whether these changes are related or unrelated to the toxemia. These data are summarized in Table I.

TABLE I. CEPHALIN-CHOLESTEROL FLOCCULATION, THYMOL TURBIDITY, AND BROMSULFALEIN TESTS DURING PREGNANCY AND THE EARLY PUERPERIUM AND DURING THESE SAME STATES COMPLICATED BY ECLAMPSIA, PRE-ECLAMPSIA, AND HYPERTENSIVE DISEASE

TEST	NORMAL (NO.)	NORMAL PREGNANCY (NO.)	COMPLICATED PREGNANCY (NO.)	NORMAL POST PARTUM (NO.)	COMPLICATED* POST PARTUM (NO.)
Cephalin-cholesterol flocculation					
plus					
0-1	5	24	13	6	9
2-3	3	2		3	
4-5		1	1	1	
Over 6					1
Totals	8†	27	14	10	10
Thymol turbidity units					
1	1	11	3	3	4
2	3	5	5	2	4
3	3	8	3	1	2
4	1	3	2	4	
5	1				
6					
7			1		
Totals	9	27	14	10	10
Bromsulfalein, per cent					
0.0- 2.0	7	7	8	7	2
2.0- 4.0	1	11	1		1
4.0- 6.0	1	12	1	1	1
6.0- 8.0		4	1	1	
8.0-10.0		2	1		2
10.0-Up			2		4
Totals	9	36‡	14	9†	10

*The complication occurred ante partum.

†One lost in processing.

‡Includes 12 used in dosage study; three of other normals have no bromsulfalein recorded.

Applying in principle sequential analysis[16] to these data, it is not too probable that the cephalin-cholesterol flocculation and thymol turbidity tests will be abnormal in more than a small percentage of any series of eclamptics and pre-eclamptics as usually cared for and treated in this clinic.[17, 18]

The data on bromsulfalein collected here seem to indicate some tendency for the normal pregnant woman to excrete bromsulfalein less rapidly than the normal nonpregnant woman. However, the difference between the means of the data from the nonpregnant and the pregnant groups presented here is not particularly significant; the ratio of the difference between the means to the standard deviation of the means being 2.44 assuming both sets of data to approximate the same type of distribution. A larger series of cases must be accumulated before any definite conclusion can be drawn. The data in the previous literature on this subject, which can be traced from the paper of Cantarow, Stuckert and Gartman,[19] indicate no increased retention of bromsulfalein by the normal pregnant woman. Our data are summarized in Table I.

As could be expected from the data in the literature and in agreement with it, some of the eclamptics and pre-eclamptics retained more bromsulfalein than normal. However, this retention did not correlate with the values obtained with the cephalin-cholesterol flocculation or the thymol turbidity tests but seemed to be independent of them. These data are summarized in Table II.

TABLE II. BROMSULFALEIN TEST IN ECLAMPSIA, PRE-ECLAMPSIA, AND HYPERTENSIVE DISEASE

PER CENT	ECLAMPSIA (NO.)	SEVERE PRE-ECLAMPSIA ANTE PARTUM (NO.)	SEVERE PRE-ECLAMPSIA POST PARTUM (NO.)	MILD PRE-ECLAMPSIA ANTE PARTUM (NO.)	MILD PRE-ECLAMPSIA POST PARTUM (NO.)	HYPERTENSIVE DISEASE (NO.)
0.0- 2.0	1	3		2	1	2
2.0- 4.0				2	1	
4.0- 6.0				1		
6.0- 8.0		1				
8.0-10.0	1	1	1			
10.0-Up	2	1	1		2	
Totals	4	6	2	5	4	2

Comment

Our negative findings with respect to the cephalin-cholesterol flocculation test in pregnancy complicated by toxemia are not in accord with the findings of Philpott, Handelman, and Primrose,[20] who report positive cephalin-cholesterol flocculation tests in 11 of 33 toxic cases. This difference might, however, be due to differences in methodology, in the time the test was performed, in patients, or in the care and treatment of the patients.

The suggestion contained in these data that there is a tendency for a retention of bromsulfalein in the normal pregnant woman needs further evaluation, particularly so in view of the findings of Munnell[21] using the Bradley technique[14] of a normal effective hepatic blood flow in normal pregnancy. The question has also been raised as to whether bromsulfalein measures only liver function since bromsulfalein is reported to be removed from the blood of eviscerated, hepatectomized, nephrectomized dogs.[22]

Summary

Liver function as measured by the cephalin-cholesterol flocculation and thymol turbidity tests has been determined in normal and complicated pregnancy and has been compared with the bromsulfalein test performed simultaneously. The cephalin-cholesterol and the thymol turbidity tests were normal in both normal pregnancy and during eclampsia and pre-eclampsia. Contrarywise, bromsulfalein was retained by some during eclampsia and pre-eclampsia as has been reported previously by others.

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530 EAST 70TH STREET

AN ANALYSIS OF 131 CASES OF TRANSVERSE PRESENTATION

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THIS study covers 131 cases of transverse presentation occurring in the Johns Hopkins Hospital from April 1, 1931, through Dec. 31, 1948. It supplements the earlier report by Eastman, who studied 147 cases in this hospital from August, 1896, to April, 1931. The purpose of this study is to ascertain whether there has been any improvement in the fetal mortality rate of transverse presentation; and to find the possible causes of any such improvement.

As in the previous series, cases in which the fetus assumed a longitudinal presentation in labor, either spontaneously or through manipulation, as well as cases occurring in twin pregnancies, were omitted. All cases of transverse presentation, irrespective of fetal weight, were included in this series. Eight babies weighed less than 1,500 grams, including one infant of 965 grams; ninety-one fetuses were classified as mature (2,500 grams or more). Eleven infants weighed more than 4,000 grams.

Since 1932, analyses of series of transverse presentations have been published by Torpin (1940), Novey and Schneider (1941), Cole and Delany (1946), and Johnson (1949). These papers, combined, cover 439 transverse presentations, with a gross fetal mortality of 49.2 per cent and a maternal loss of 5.9 per cent.

Etiology of Transverse Presentation

Ninety-one of the patients in this series had fetuses of 2,500 grams or more. Among these patients, the presumable cause of the abnormality is shown in Table I.

TABLE I. ETIOLOGIC FACTORS IN 91 CASES OF TRANSVERSE PRESENTATION WITH INFANTS WEIGHING 2,500 GRAMS OR MORE

FACTOR	NO.		PER CENT	
1. Multiparity (one or more previous infants)				
(a) 3 or more previous infants		50		54.9
(b) 6 or more previous infants		30		33.3
(c) 9 or more previous infants				
2. Contracted inlet (conjugate diameter than 11.5 cm.)	20		21.9	
(a) White		5		5.5
(b) Negro		15		16.5
3. Pelvic neoplasms	11		12.1	
4. Excessive size of the fetus (over 4,000 grams)	11		12.1	
5. Placenta previa	7		7.6	
6. Previous suspension of the uterus	4		4.3	
7. Malposition of the uterus	2		2.2	
8. Arcuate uterus	1		1.1	

Multiparity, as in the previous series, again plays a leading role in predisposing to transverse presentation. Fifty, or 54.9 per cent, of the mothers with the mature babies had three or more previous pregnancies. During a similar period, only 29.02 per cent of the clinic population at large consisted of patients of that parity. Moreover, the present series contains twelve mothers who had nine or more previous infants, or 13.2 per cent. The clinic population during a similar period showed only 4.1 per cent of mothers of this parity.

On the other hand, inlet contraction did not exert a significant influence in the causation of transverse presentation in this group. In the clinic population at large, this factor was present in 32.9 per cent of the Negro patients and 10.0 per cent of the white patients, compared to 16.5 and 5.5 per cent, respectively, in the transverse group.

In the previous series, six of ninety-one mothers who had mature fetuses had had suspension operations, conceivably resulting in malposition of the uterus. This factor continues to be of importance. In addition, one mother in the present group had had a previous Watkins interposition operation, without tubal ligation.

Among the forty cases in which the infants weighed between 900 and 2,500 grams, the causative factors are shown by Table II. Comparison with the general clinic figures again shows multiparity as a prominent factor.

TABLE II. ETIOLOGIC FACTORS IN 40 CASES OF TRANSVERSE PRESENTATION WITH INFANTS WEIGHING LESS THAN 2,500 GRAMS

FACTOR	NO.	PER CENT
1. Multiparity (one or more previous infants)	33	82.5
(a) 3 or more previous infants	24	60.0
(b) 6 or more previous infants	15	37.5
(c) 9 or more previous infants	4	10.0
2. Placenta previa	13	32.5
3. Inlet contraction	8	20.0
(a) White	2	5.0
(b) Negro	6	15.0
4. Small macerated fetus	4	10.0

It is interesting to study the patients who had repeated transverse presentations. In this series there were nine such patients, with a total of twenty deliveries. Among these patients, four, with nine deliveries, had contracted pelves; two, with four deliveries, had very relaxed abdominal walls (one being a grand multipara). Of the remainder, one had an arcuate uterus, one had very taut round ligaments which interfered with the longitudinal development of the uterus, and one had extensive pelvic adhesions.

Maternal Mortality

In 131 cases there were four maternal deaths, an incidence of 3.05 per cent. Brief histories of these four fatal cases are as follows:

CASE 1.—No. 35856. The patient was a 39-year-old, unregistered, white, para vi, with six living children, whose estimated date of confinement was April 18, 1931. Pregnancy progressed normally until one month before admission, when occasional slight vaginal bleeding occurred. On March 3, 1941, the patient had a profuse vaginal hemorrhage at home. Upon admission she had a blood pressure of 90/60, pulse 104, and hemoglobin 50 per cent. A sterile vaginal examination revealed partial placenta previa and transverse presentation. A cesarean hysterectomy was done, the patient receiving 550 c.c. of blood during the operation. A viable infant weighing 2,300 grams, which died subsequently, was obtained.

Postoperatively, the patient did well at first. However, she later developed bronchopneumonia and then thrombophlebitis in the right thigh. She suddenly expired on the forty-first postoperative day, apparently as a result of pulmonary embolism. Autopsy was refused.

CASE 2.—No. 56936. This was a 21-year-old, Negro, unregistered, para iii, with three living children, whose estimated date of confinement was Oct. 12, 1934. The patient did well until July 27, 1934, when uterine contractions began. Shortly thereafter the membranes ruptured, and the left arm and umbilical cord prolapsed. A physician performed some internal manipulation, and then sent the patient to the hospital. She arrived in the hospital after eight hours of labor, with active uterine contractions and a definite transverse presentation. The blood pressure was 120/70, pulse 100, and temperature 100.2° F. Examination under ether anesthesia revealed full dilatation of the cervix. The prolapsed arm was amputated and a 3,350 gram stillborn fetus delivered by a very easy version and breech extraction. During the version the pulse rose to 180. The placenta was manually removed with ease. There was minimal external bleeding. Following this procedure, the patient suddenly expired, after a total of twenty minutes of anesthesia.

At autopsy a right-sided lower uterine segment rupture was discovered, with a huge hematoma extending into the broad ligament.

CASE 3.—No. 110145. The patient was a 32-year-old, Negro, registered, para iii, with two living children, who had a generally contracted rachitic type of pelvis. Her estimated date of confinement was about October, 1937. She had twice previously been delivered by classical cesarean section, the indication each time being transverse presentation. A transverse presentation was again diagnosed on July 8, 1937. On Aug. 11, 1937, the patient experienced sharp lower abdominal pain and tenderness. Rupture of the previous cesarean scar was suspected, and an elective classical cesarean section with Madlener sterilization was done. At operation a 5 cm. subperitoneal separation of the old scar was found. A loop of ileum was adherent to the anterior surface of the uterus and was freed at operation. A 1,925 gram viable infant was obtained.

Postoperatively, the patient suffered from abdominal distress and obstipation. Despite parenteral fluids and gastric drainage her condition deteriorated. On the fifth postoperative day a laparotomy was performed. The loop of ileum which previously had been adherent to the anterior surface of the uterus was found to have assumed its former position. Proximal to this point of adhesion the intestine was dilated; distal to it the bowel was deflated. The adhesions were released, and the abdomen closed. Postoperatively the patient had extreme pyrexia (temperature 108.4° F.) and she expired within eight hours.

At autopsy the loop of small bowel was again discovered to be adherent to the anterior surface of the uterus.

CASE 4.—No. 170495. The patient was a 42-year-old, white, para iv, with three living children, whose estimated date of confinement was approximately in September, 1939. She was a private patient of one of the senior attending staff. In October, 1937, she had had a Watkins interposition operation with cervical amputation. Tubal ligation was not performed. The menstrual periods never recurred. In October, 1938, the patient had an episode which may have been an abortion. Pregnancy occurred in 1939. The gestation was complicated by chronic and severe urinary retention and infection. The patient refused therapeutic abortion. On Sept. 20, 1939, she was admitted because of nausea, vomiting, and abdominal pain. The infant lay in transverse presentation. On Sept. 22, 1939, a classical cesarean section and Pomeroy tubal sterilization were performed. A 2,590 gram viable infant was obtained. During and after the operation the patient received ample transfusion therapy. Nevertheless, postoperatively, she had severe nausea and vomiting and a wound infection as well as acute right-sided pyelonephritis. The abdominal wound disrupted on the twelfth postoperative day. A secondary closure was performed, using silver wire. Postoperatively, the patient was treated with sulfapyridine, digitalis, and an

oxygen tent. Her blood culture showed hemolytic *Staphylococcus aureus* and her urine showed *Bacillus coli communis*. Despite all measures the patient expired on the nineteenth postoperative day.

At autopsy the findings included secondary wound infection, ascites, purulent endometritis, thrombophlebitis of the right ovarian vein, hydronephrosis and hydroureter on the right side, hydrothorax, left, and atelectasis of the left lower lobe.

Comment.—In contrast to the previous series, only two of the four maternal deaths occurred with premature infants. One patient had been subjected to possibly unsterile vaginal manipulations at home; one patient had intestinal obstruction following three cesarean sections; one patient had had a previous interposition operation, with resultant urinary infection; and in the last patient placenta previa was a factor, but death was a sequel to peripheral venous thrombosis. The most recent death occurred in 1939. In only one case (Case 2) was the transverse presentation a major factor in the outcome of the case.

Fetal Mortality

Table III shows the fetal mortality in all cases in which the fetus weighed 2,500 grams or more, compared with the similar figures in the previous study. Table IV shows the fetal mortality in cases in which the fetus weighed less than 2,500 grams.

TABLE III. FETAL MORTALITY IN MATURE INFANTS

	OLD SERIES			NEW SERIES		
	CASES	DEATHS	FETAL MORTALITY	CASES	DEATHS	FETAL MORTALITY
1. Total	93	44	47.2%	91	20	21.9%
Fetal heartbeat present on admission	70	21	30.0%	83	12	14.3%
Delivered vaginally	49	21	42.8%	33	11	33.3%
Delivered by section	21	0	0.0%	50	1	2.0%
2. Total registered	57	16	27.6%	64	13	20.3%
Fetal heartbeat present on admission	54	14	26.0%	60	9	15.0%
Delivered vaginally	38	14	37.0%	22	8	36.4%
Delivered by section	16	0	0.0%	38	1	2.7%
3. Total unregistered	36	28	77.0%	27	7	25.9%
Fetal heartbeat present on admission	16	7	43.0%	23	3	13.0%
Delivered vaginally	11	7	64.0%	11	3	27.3%
Delivered by section	5	0	0.0%	12	0	0.0%

TABLE IV. FETAL MORTALITY IN PREMATURE INFANTS

	CASES	DEATHS	FETAL MORTALITY
Total	40	24	60%
Fetal heartbeat present on admission	31	16	51.6%
Delivered vaginally	18	12	66.6%
Delivered by section	13	4	30.8%

The reduction of fetal mortality in the more recent series is very striking, and is statistically significant. It is particularly notable in the unregistered patients. The number of cases treated by cesarean section has increased by 100 per cent. The over-all fetal mortality in this new series, however, remains excessively high. Although the cesarean section mortality approaches that which is generally acceptable, there has been no significant change in the mortality of babies delivered vaginally.

The Causes of Fetal Mortality

In this series there were forty-four fetal deaths, an over-all mortality of 33.5 per cent. As previously noted, fetal mortality was much higher in the cases delivered vaginally. Deaths in the latter group would be more likely to be those peculiar to transverse presentation. Tables V and VI show factors concerned in the fetal deaths in this series.

TABLE V. FACTORS CAUSING OR CONTRIBUTING TO DEATH IN 16 INFANTS WITH FETAL HEARTBEAT ABSENT ON ADMISSION

FACTOR	BELOW 2,500 GRAMS (8)	2,500 GRAMS AND OVER (8)	TOTAL	PER CENT
Prolapsed extremity	6	2	8	50.0
Unsterile manipulations	1	3	4	25.0
Toxemia	1	3	4	25.0
Prolapsed cord	2	1	3	18.1
Congenital syphilis	1	1	2	12.5
Placenta previa	1	0	1	6.3
Abruptio placentae	1	0	1	6.3
Maternal diabetes	0	1	1	6.3
Maternal heart disease	0	1	1	6.3

In Table VI, prematurity was reckoned as a possible contributory cause in the deaths of all living infants weighing less than 2,000 grams at delivery. The term "anoxia complex" refers to the group of infants showing petechial hemorrhages in pleura, epicardium, and other viscera at autopsy. It should be noted that two of the fetuses delivered vaginally, in whom the fetal heartbeat was thought to be present on admission, were macerated. Presumably the diagnosis of a living fetus in these cases was erroneous.

TABLE VI. FACTORS CAUSING OR CONTRIBUTING TO DEATH IN 28 INFANTS WITH FETAL HEARTBEAT PRESENT ON ADMISSION

	BELOW 2,500 GRAMS (16)		2,500 GRAMS AND OVER (12)			
FACTOR	STILLBORN (5)	LIVEBORN (11)	STILLBORN (11)	LIVEBORN (1)	TOTAL	PER CENT
Prematurity	0	10	0	0	10	35.7
Prolapsed extremity	0	0	7	0	7	25.0
Prolapsed cord	1	2	4	0	7	25.0
Placenta previa	1	4	1	0	5	17.9
Intracranial hemorrhage	0	2	3	0	5	17.9
Atelectasis	0	4	1	0	5	17.9
Toxemia	1	0	2	0	3	10.7
Anoxia complex	0	2	0	0	2	14.2
Maceration (error)	1	0	1	0	2	14.2
Pneumonia	0	0	0	1	1	7.1
Gross anomalies	0	0	1	0	1	7.1

Among the commonest complications of these fatal cases were those associated with premature or early rupture of the membranes. The role of early rupture of the membranes is illustrated by Tables VII and VIII. The fetal mortality varies directly with the duration of time between rupture of the membranes and delivery; and inversely with the degree of dilatation of the cervix at the time of rupture. Early rupture of the membranes exerts a decidedly unfavorable influence on the fetal outcome. As in the previous series, prolongation of labor had an unfavorable influence upon the fetal mortality in transverse presentation and exceeded 60 per cent when labor lasted longer than

twenty-four hours. No significant difference in fetal mortality was observed between the white and Negro races. There were twenty fetal deaths in sixty-three white mothers, and twenty-four fetal deaths in sixty-eight Negro mothers.

TABLE VII. RELATION OF RUPTURE OF MEMBRANES TO CERVICAL DILATATION IN 64 VAGINAL DELIVERIES

TIME OF RUPTURE OF MEMBRANES	CASES	STILLBORN	DISCHARGED DEAD	FETAL MORTALITY
Before onset of labor, to 5 cm. dilatation	32	20	2	68.2%
From 5 cm. dilatation to full dilatation	31	13	2	48.4%
Unknown	1	0	0	0.0

TABLE VIII. RELATION OF TIME OF RUPTURE OF MEMBRANES TO FETAL MORTALITY IN 64 VAGINAL DELIVERIES

TIME OF RUPTURE OF MEMBRANES	CASES	STILLBORN	DISCHARGED DEAD	FETAL MORTALITY
From immediately before delivery to 3 hours before delivery	28	9	2	39.3%
More than 3 hours before delivery	32	21	1	68.8%
Unknown	4	2	1	75.0%

Methods of Treatment

Fifty-four patients were delivered by some type of internal version. Subtracting four patients who had destructive operations in addition, and four more in whom the fetal heartbeat was inaudible on admission, there were eighteen fetal deaths in forty-six cases, a mortality of 39.1 per cent. One mother died following version and rupture of the uterus, a mortality of 1.85 per cent.

Sixty-three patients who had fetal hearts audible on admission were delivered by cesarean section. Five of these infants were lost, a mortality of 7.01 per cent. All five infants were delivered under ether anesthesia and were markedly asphyxiated at birth. All five died of respiratory complications. Three mothers, or 4.8 per cent, died following cesarean section, but only one of these deaths was primarily due to the operative procedure.

Voorhees bags were inserted in eighteen cases. Eight bags were inserted intraovularly, nine extraovularly, and one in the vagina. In five cases, or 27.8 per cent, intrapartum infection occurred. In three cases, or 16.6 per cent, postpartum infection was present. In five cases, or 27.8 per cent, the bag failed to produce satisfactory cervical dilatation. Three babies were dead before bags were inserted. In the remaining fifteen cases, three, or 20 per cent, of the infants succumbed.

Destructive operations were performed upon five infants. All of these babies were dead before the procedure was undertaken.

The management of the primigravidous patients in this series deserves separate comment. There were twenty such mothers, eleven Negro and nine white. Of these, thirteen fetuses were mature and seven premature. Among the former, all had the fetal heartbeat present on admission. Three were delivered by version and extraction, and all were born dead. The remainder were all discharged alive, having been delivered by cesarean section. Of the seven premature infants, five had the fetal heartbeat present on admission. Among these five, two were delivered by section and discharged alive. The remainder were all delivered by internal version. Two were stillborn and one died after delivery.

Comment

Unquestionably section should be the method of choice in treating transverse presentation in primigravidas with viable infants, as well as patients in whom mechanical obstruction is present in the birth passages. In multiparous patients in early labor, especially if premature early rupture of the membranes has occurred, cesarean section is also the method of choice. The rapidly rising fetal mortality in prolonged labors and in cases of prolonged rupture of the membranes militates against expectant treatment in these cases. In the patient seen late in labor, with a viable fetus, and intact membranes, version and extraction at full dilatation are indicated. In such cases, an extraovular uterine bag may sometimes be employed to advantage until full dilatation is reached. The neglected case, with prolapsed arm, impacted shoulder, and dead fetus is best treated by decapitation. If possible, transverse presentation should be corrected by external manipulation if it is recognized in the antenatal period.

Summary

1. In 131 cases of transverse presentations studied at the Johns Hopkins Hospital, there were four maternal deaths, an incidence of 3.05 per cent and forty-four fetal deaths, an incidence of 33.5 per cent. In the eighty-three cases in which the infants were mature and in which the fetal hearts were audible on admission, the total fetal mortality was 14.3 per cent.

2. Only one of the four maternal deaths was directly related to the transverse presentation. The remainder were due to intercurrent infections (two deaths) and intestinal obstruction.

3. The fetal mortality of the cases in which the fetus weighed 2,500 grams or more was only half as great as in the previous series reported from this hospital. Over twice as many patients were treated by cesarean section in the present group as in the group reported previously by Eastman.

4. Among the fetal deaths in vaginally delivered babies more than half had prolapse of an extremity; over one-third had prolapsed cord. These accidents are generally attributed to premature rupture of the membranes. Prolongation of labor, especially following rupture of the membranes, was attended by a striking increase in fetal mortality.

5. In nearly one-third of the cases in which they were used, Voorhees bags failed to produce satisfactory cervical dilatation. In a similar number of cases, intrapartum infection occurred.

6. Cesarean section should be the procedure of choice in all patients with transverse presentation of mature viable fetuses early in labor. A patient late in labor, with a viable fetus, may still be treated to advantage by version and extraction at full dilatation.

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HEMORRHAGE FROM RUPTURED UTEROOVARIAN VEINS DURING PREGNANCY

Report of Three Cases and Review of the Literature

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MASSIVE hemorrhage from ruptured uteroovarian veins during pregnancy is an overlooked cause of sudden maternal death. Diagnosis is difficult because there is usually no traumatic incident to account for concealed hemorrhage of such proportions. Little help can be obtained from standard obstetric textbooks because often no consideration is given to complications involving this system of veins. Indecision and tragic delay have resulted from unfamiliarity with this syndrome. Treatment must be aggressively initiated.

This report is based upon the cases of three obstetrical patients whose pregnancies were complicated by intra-abdominal bleeding from the uteroovarian venous system. A complete review of the literature revealed seventy-two similar cases. Analysis of the entire group disclosed important diagnostic and etiological factors not previously emphasized.

Bleeding was of three types: intraperitoneal, retroperitoneal, and a combination of intra- and retroperitoneal bleeding. Hemorrhage from vessels distributed over the surface of the uterus was usually entirely intraperitoneal. The firm attachment of the visceral peritoneum to the myometrium prevented subperitoneal dissection of the hematoma and free intraperitoneal bleeding resulted. Rupture of the veins located between the folds of the broad ligament and in the areolar tissue of the posterior retroperitoneal space resulted in enormous hematomas extending from the thoracic to the pelvic diaphragms. Occasionally pressure of the dissecting clot caused a secondary rent in the peritoneum. In such instances both intraperitoneal and retroperitoneal bleeding occurred.

The initiating symptom was severe abdominal pain. Generalized peritoneal irritation was evident if bleeding occurred into the peritoneal cavity. Confined retroperitoneal bleeding was usually associated with unilateral abdominal and back pain. Shock usually quickly dominated the picture in either instance. If hemorrhage was associated with the pain of labor, the first apparent clinical manifestations were those of shock. It is essential to recognize that uteroovarian veins may rupture spontaneously during normal pregnancy and uncomplicated labor. It is probable that some instances of "obstetrical shock" are on this basis.

Three patients demonstrating slightly different clinical manifestations of this condition are presented.

CASE 1.—M. B., No. 155233, aged 24 years, white, primigravida, was first seen in the prenatal clinic on Nov. 22, 1930, and gave her last menstrual period as Aug. 1, 1930. The estimated date of confinement was May 8, 1931. Prenatal studies were within normal limits and the history was essentially negative. Because of the financial depression she transferred to the Welfare Department of the City of Detroit in December, 1930, and delivered at home.

On May 13, 1931, at 10:00 P.M., she was admitted to the emergency room of the Henry Ford Hospital suffering from severe shock. At 7:30 A.M. that day, after an uneventful nine-hour labor, she had delivered spontaneously a normal 8½ pound infant. Her immediate postpartum course was uneventful until about 7:00 P.M. when she was seized with a sudden, severe pain in the right lower abdomen. Nausea and vomiting soon followed and she lost consciousness for a short period of time.

Examination showed the patient to be suffering from profound shock with the blood pressure unobtainable and the pulse barely palpable at 132 per minute. There was no increased vaginal bleeding. In spite of administration of 1,900 c.c. of blood and 1,000 c.c. of 10 per cent glucose solution intravenously, the patient rapidly failed and expired eighteen hours after admission.

Autopsy disclosed the peritoneal cavity to contain 1,000 c.c. of blood. In addition, there was a large bloody mass occupying the right posterior retroperitoneal space extending from the pelvic floor to the thoracic diaphragm. The main part of this mass weighed 2,200 grams. The uterus was normal. On section, the right ovarian vein was torn across at a distance of 6 cm. from the uterus and 2 cm. from a bifurcation. The uterine vessels were intact.

CASE 2.—H. B., No. 4311856, aged 35 years, Negro, gravida vi, para iv, was first seen in the Henry Ford prenatal clinic Sept. 19, 1947, at which time she was three months pregnant. The estimated date of confinement was March 22, 1948. She gave the history of treated syphilis in 1936, although at this time (1947) the serological tests were negative for evidence of latent syphilis. Her prenatal course was considered uneventful. At about 4:00 A.M., Feb. 22, 1948, labor began and she delivered spontaneously at 5:45 A.M. A first-degree laceration of the perineum was repaired under nitrous oxide-oxygen anesthesia lasting fifteen minutes.

The patient failed to react from the anesthetic, became restless, and showed evidence of shock. The uterus was firmly contracted and there was no unusual vaginal bleeding. Efforts to administer intravenous therapy were impossible because of venous collapse. Sternal administration of plasma was instituted but the patient expired at 7:25 A.M.

Autopsy disclosed the peritoneal cavity to contain 2,000 c.c. of fresh blood and there was a large hemorrhage distributed from the pelvic floor to the level of the right adrenal gland in the space posterior to the peritoneum on the right. Just inferior to the appendix was a rent in the peritoneum measuring 3.5 cm. The volume of the posterior peritoneal hemorrhage was estimated at 1,000 c.c. The uterus was normal. The precise point of rupture was not discovered, although the final diagnosis was intraperitoneal and retroperitoneal hemorrhage principally in the region of the right ovarian vein. The right ovarian artery was intact.

CASE 3.—D. B., No. 105475, aged 20 years, primigravida, presented herself in January, 1944, for prenatal care at Fitzsimmon's General Hospital, Denver, Colorado. Prenatal studies were considered normal until the thirty-sixth week of gestation when she was admitted to the hospital in active labor. The estimated date of confinement was June 19, 1944. After eight hours and ten minutes of moderate labor, she was delivered under fractional caudal anesthesia with the aid of low forceps and medial episiotomy. The viable infant weighed 4 pounds, 15 ounces. Her postpartum course was uneventful until the fourteenth day when she was seized with a severe pain in the right flank and right lower abdominal quadrant. Examination revealed moderate muscle spasm with exquisite tenderness on pressure. After twenty-four hours the tenderness subsided and a mass could be palpated

extending from the lower pole of the right kidney to the brim of the pelvis. The mass was excised from the right posterior retroperitoneal space on June 6, 1944. The ovarian vessels were found to enter the inferior pole of the tumor and emerged from the medial side at the level of the inferior pole of the kidney. Superiorly, the hematoma almost completely enveloped the kidney, and medially had wrapped itself around the ureter. Dissection was accomplished without excessive bleeding. The postoperative course was uneventful. Pathological examination of the hematoma showed it to measure 18 by 8 by 5 cm. It was well encapsulated. On section oval and round spaces filled with clotted blood were encountered. The ovarian vessels were identified passing through the center of the mass. Microscopic sections showed the mass to be composed of saccular varices containing clotted blood. The vein wall was excessively thin and points of rupture could be identified. The largest varix measured 5 by 2 cm. The final pathological diagnosis was phlebectasia with saccular and fusiform outpouchings and organizing thrombi.

Comment

In 1904, J. Whitridge Williams[1] reviewed the literature on hemorrhage from the uteroovarian veins as a complication of pregnancy. He cited thirty-one previously reported cases and added one of his own. Williams noted the first reported case was one observed by Baudelocque, reported by Casaubon in 1778. Since 1904, a number[2-23] of excellent but incomplete reviews have appeared in the literature, and for the most part Williams' report has been overlooked. Greenhill,[14] in commenting on a report by Pineda, stated in *The 1943 Year Book of Obstetrics and Gynecology* that only fourteen cases associated with pregnancy had been reported.

It is probable that in many instances the correct diagnosis is not made. Because of technical reasons, both at the time of operation and autopsy, it is difficult to locate the precise point of hemorrhage. D'Errico,[23] in 1933, cited six cases of extensive intra-abdominal hemorrhage following labor for which no cause was found. Because the condition is rare, most reports treat this subject as a medical curiosity rather than a complication essentially peculiar to pregnancy.

Etiology

The reason why uteroovarian veins rupture during pregnancy is speculative. Analysis of the reported cases showed that only 60 per cent were directly related to labor. Instances have been reported where hemorrhage occurred as early as at 10 weeks' gestation and as late as twenty-one days post partum. Williams emphasized the unimportance of traumatic parturition as an etiological factor. Operative delivery was noted in only six instances. The average age was 28.6 years and 55.4 per cent of the patients were primiparous. The average infant weight was less than 7 pounds.

A number of authors have mentioned varicose veins of the broad ligament as an important finding at operation and autopsy. Varicose veins of the vulva are commonly encountered during pregnancy and a number of instances of serious hemorrhage have been reported. Although the incidence and degree of varicose involvement of the uterine and ovarian veins during pregnancy is not known, the third case herein reported is an example of the extreme degree of phlebectasia which may occur. Sites of rupture in order of their frequency were as follows: right 28, left 19, posterior surface of the uterus 11, anterior surface of the uterus 2. In eighteen patients the point of rupture was completely obscured by extensive hemorrhage.

Venous Pressure.—Generally recognized is the physiological increase in functional demand placed upon the pelvic vascular system by pregnancy, so well demonstrated by simple observation of the veins during cesarean section. Such extensive physiological hypertrophy is difficult to distinguish from true

varicosities by clinical observation. Other than recognition of the fact that the venous load carried during pregnancy is greatly increased, to our knowledge, no extensive physiological studies have been performed on the ovarian and uterine veins. Burwell,[24] in 1938, in his studies on circulation of the placenta, demonstrated alterations in venous pressure during pregnancy. He pointed out that in the nonpregnant state the venous pressure of the arms and legs was practically identical. On the other hand, during pregnancy the venous pressure in the femoral vein rose from 100 to 200 mm. of water higher than in the arms. This was two to three times higher than normal. In animal experiments with pregnant bitches he showed that the venous pressure changes were not due to increased intra-abdominal pressure and could only partially be explained by pressure of the pregnant uterus on the veins. Moreover, Burwell stated that the venous pressure in animals increased as the point of measurement approached the placenta. He felt that these findings suggested that the placenta functioned as an arteriovenous fistula. Posture, muscular activity, and respiratory activity all influence venous pressure, and these factors appeared to be of particular significance to the venous system draining the pregnant uterus. In the nonpregnant state extremely high venous pressures have been recorded during the Valsalva experiment which consists of expiratory effort with the chest in the inspiratory position and the glottis closed. The Valsalva experiment duplicates many efforts to strain, such as lifting heavy weights, sudden muscular activity, staining at stool and labor. In the forty-four patients whose symptoms came on in relation to labor the strain of labor may have been a factor.

Analysis of the records of patients whose symptoms were unrelated to labor yields information suggesting that sudden increase in venous pressure may have been an important contributing factor. Twenty-eight patients comprise this group. In fourteen patients the symptoms apparently came on spontaneously for no known reason, while fourteen developed symptoms closely related to some form of muscular activity which could be interpreted as straining. In 1824, Chausser[1] reported a patient who developed the pain of rupture of the veins during a rough ride in a wagon. Falk's[6] patient complained of a sensation of tearing during a sudden movement. Two patients[2, 8] were eating, another housecleaning,[20] and Eylert's[12] patient lifted her 2-year-old child. Eylert was of the opinion that increase in venous pressure associated with the strain of lifting possibly accounted for rupture of the vein in this instance. Defecation accounted for the onset of symptoms in two[15, 5] patients and Modiano's[25] patient arose from bed to urinate. Balch and Green[21] reported a patient suffering from a severe cough who developed prepartum bleeding from a ruptured vein. Coitus was listed as the inciting factor in three patients. Potacki's[4] patient was ten weeks pregnant, Harding and Concanon's[3] 25 weeks, and the patient reported by Kenny and Doniach[9] 36 weeks. Intercourse was accomplished three times in one night by the latter's patient and symptoms came on during the last sexual act. She expired before operation could be performed. A post-mortem cesarean section yielded a living child.

Studies in progress indicate that the venous pressure in the superficial veins of the extremities and the ovarian veins respond in an identical fashion to similar influences. The erect posture and strain efforts influence the pressure to rise. Increased venous pressure in connection with inherent vein-wall weakness appears to be an important factor predisposing to rupture.

Diagnosis

Sudden onset of severe lower-abdominal pain rapidly followed by shock constituted the main points in diagnosis. Bleeding confined to either posterior

retroperitoneal space localized the symptoms to either the right or left side. In approximately 50 per cent of the patients, peritoneal irritation developed due to the presence of hemoperitoneum.

Labor frequently obscured the diagnosis and shock may be the only evidence suggesting hemorrhage. The second patient herein reported illustrated this point because her symptoms apparently began during the second stage of labor during the time she was under anesthesia. Before she had sufficient time to recover from the anesthetic, her condition became so serious that she was unable to localize her subjective symptoms. Restlessness and profound shock were the only factors suggesting internal hemorrhage. Differential diagnosis must include rupture of the uterus and premature separation of the placenta.

Prognosis

The mortality rate for patients reported was 49.3 per cent. The outlook was best for those patients whose symptoms came on unrelated to labor as twenty-one of thirty such patients recovered (70 per cent). Labor increased the hazard as 76.3 per cent of this group died. There were six intrapartum deaths.

Treatment

The therapeutic measures for the treatment of shock from hemorrhage are well known. Based upon the amount of blood found in the peritoneal cavity and posterior retroperitoneal spaces in the first two patients herein reported, over 3,000 c.c. were required in each instance. Rapid replacement of blood loss and arrest of hemorrhage are essential.

In cases of prepartum bleeding, cesarean section to facilitate abdominal exploration was practically always necessary. Ligation of the ruptured vein was at times possible. Hysterectomy interrupts the physiological demands placed upon the uterine and ovarian veins and has been used several times with success when the precise point of rupture could not be identified. Adequate antibiotic therapy to combat infection is necessary as some patients survived the initial blood loss to die later of infection of the hematoma.

Summary

1. The basis for this paper is the presentation of case records of three obstetrical patients, each suffering a similar serious complication of pregnancy. In each instance rupture of the uteroovarian veins accounted for the syndrome. Massive hemorrhage resulted in sudden death of two patients, while one survived. One patient recovered after resection of a large posterior retroperitoneal hematoma arising from varices of the right ovarian vein.

2. The literature yields seventy-two similar cases. One gains the impression that some instances of "obstetrical shock" of unknown origin and sudden maternal death due to intraperitoneal hemorrhage may be on this basis.

3. Increased venous pressure in the ovarian and uterine veins, greatly dilated in response to the physiological demands of pregnancy, appears to be an important contributing cause to rupture. The strain of labor and other forms of muscular activity which cause a rise in venous pressure appear more important as etiological factors than the actual trauma of labor.

4. Treatment is primarily aimed at replacing and maintaining blood volume and arrest of hemorrhage.

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THE POMEROY METHOD OF STERILIZATION*

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IT IS not our purpose in presenting this paper to discuss the very grave problem of sterilization for eugenic or economic reasons. It is mentioned here, however, because there are a few cases in this series where the eugenic or economic problems unquestionably influenced our decision to perform the operation, not as a primary factor, but secondary to what we considered a medical problem. Since 1924, over a period of twenty-five years, we have used the Pomeroy technique routinely for sterilization in women admitted to our Division. On two occasions, once in 1933 and again in 1939, we reported our results. In this communication, we are reporting our results in the last ten years, together with a statistical summary of our experience with this operation in 1,550 cases, covering a period of twenty-five years. We decided to institute this technique as a routine after we had had several failures with various other types of sterilization operations, including cornual resections of the tubes. During the preceding four or five years, following World War I, we had several patients who had had salpingectomies with cornual resections performed for the purpose of sterilization who had to be reoperated upon because of the development of cystic ovaries. We elected to investigate a method employed at the Brooklyn Hospital. This method was advocated by Dr. Ralph Pomeroy and although he did not claim any originality for it, he stated that he had never seen it done. It was not placed in the literature, however, until 1929 when Bishop and Nelms[1] reported their results in 100 cases. In their series no known pregnancy had occurred. In their paper, they used the terms "simplicity," "safety," and "security."

There are very few surgical procedures which give 100 per cent results. We have heard some criticism of this very simple operation. In fact we have seen the serial sections from the resected tubal segments of a patient who afterward became pregnant and we were particularly impressed with the fact that it was necessary to cut 1,300 serial sections before the tubal lumen could be demonstrated. We would be of the opinion that in this particular case the spermatozoa were endowed with unusual persistency and vitality. Furthermore, we have operated upon one patient who had had the right Fallopian tube and the left round ligament resected. Unquestionably it is necessary to do this operation on both Fallopian tubes for it to be successful. In using this technique, the various steps in the performance of the operation, which can be done very easily and very rapidly, must meticulously be followed. Some of the im-

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portant factors involved are that the tube must be picked up at its proper place; that not too large or too small a loop is excised; that the tube is not crushed; and most important, that an absorbable ligature is used. It is with the idea of evaluating this operation after using it for twenty-five years that we report our results.

TABLE I. POMEROY STERILIZATION, 1939 TO 1949

Of the 738 patients upon whom Pomeroy sterilization was performed:
384 were performed at cesarean section
72 were performed at hysterotomy
68 were performed post partum
214 were performed at gynecologic operation
509, or 68.9%, answered the follow-up questionnaire

Table I indicates the four divisions into which fall the 738 patients upon whom a Pomeroy sterilization operation was performed. Also, the per cent of patients responding to the follow-up questionnaire is recorded. Three hundred eighty-four operations were performed at cesarean section; 72 were performed at the time of hysterotomy; 68 were performed as postpartum procedures; and 214 were performed at gynecologic operation. In this series, 509 patients, or 68.9 per cent, answered the questionnaire. Only 4, or 0.5 per cent, of our questionnaire letters were returned "unclaimed." Two hundred twenty-five, or 30.5 per cent, did not answer but we feel very decidedly that if a pregnancy had occurred, we would have heard about it. In the 30.5 per cent of patients who failed to answer questionnaire, a check with the obstetrician or gynecologist concerned confirmed the absence of further pregnancies.

The indication for the performance of this operation at the time of cesarean section was usually a repeat cesarean. The Pomeroy operations done at the time of hysterotomy were usually indicated by some chronic constitutional condition which necessitated termination of the pregnancy and the limitation of further childbearing. The Pomeroy operations performed at the time of gynecological procedures were done mainly on those patients who had extensive plastic operations performed upon the cervix and anterior and posterior vaginal walls. Usually in these patients further childbearing by the vaginal route was contraindicated since most of them already had borne several children. We believe that postpartum sterilization has a definite place in obstetric practice. During the past ten years we have thought it advisable to perform postpartum sterilization in only 68 patients.

TABLE II

Age range	15 to 52 years
Average age	32.2 years
Parity	0 to 12
Average parity	2.6
Private	429
Ward	309
Negro	81
White	657

Table II shows the age range to be from 15 to 52 years with an average age of 32.2 years. It also shows parity and the division between private and ward patients and between Negro and white patients.

Table III shows the length of time elapsing between the delivery of the patient and the sterilization operation. It varied from one hour to eleven days. During the time covered by the early part of this survey there was quite a

TABLE III. TIME OF POSTPARTUM STERILIZATION

1 hour	36
1 hour to 6 hours	5
6 hours to 12 hours	4
12 hours to 1 day	13
1 day to 3 days	4
4 days to 8 days	4
9 days to 11 days	2
Total	68

difference of opinion as to just when this operation should be done. Following Whitaker's[2] excellent work on the bacteriology of the newly emptied uterus, we now perform postpartum sterilization approximately one to two hours after delivery. We wait until we are certain that the puerperal uterus is firmly contracted and that there is no excessive postpartum bleeding. We believe that an excellent way of handling these patients is to deliver them under continuous caudal analgesia. Allowing the ureteral catheter to remain in situ, the level of the analgesia is maintained for one hour after delivery and is used as the anesthetic for the operation upon the Fallopian tubes. In the entire series all types of anesthesia were used, the majority being done under either spinal or gas-ether combination. A number of the puerperal sterilizations were done under local anesthesia.

TABLE IV. MORBIDITY

Total Pomeroy sterilizations	738	
Pomeroy sterilization, obstetrical	524	
Total obstetrical morbidity	120	or 22.9%
Pomeroy sterilization, gynecological	214	
Febrile* reaction following gynecologic operation	57	
Of the 177 febrile patients there were:		
6, or 8.8%, of the 68 performed post partum		
15, or 20.8%, of the 72 performed at hysterotomy		
99, or 25.8%, of the 384 performed at cesarean section		
57, or 26.6%, of the 214 performed at gynecologic operation		

*Not included in total of 120 obstetrical morbidity.

Table IV shows the obstetrical morbidity rate and the number of gynecologic postoperative febrile reactions. The obstetrical morbidity rate was based on the standard classification of morbidity set forth by the American Committee on Maternal Welfare. There were 524 obstetrical cases, of which 120, or 22.9 per cent, were considered morbid. There were 57 patients, or 26.6 per cent of the 214 gynecologic cases, upon whom a Pomeroy sterilization was performed who were postoperatively febrile.

TABLE V. COMBINED TOTALS OF THREE SURVEYS
1924-1933 1933-1939 1939-1949

Total obstetrical cases	50,549		
Total Pomeroy operations	941	or	1.86%
Total gynecological cases	19,160		
Total Pomeroy operations	609	or	3.17%
Total Pomeroy sterilizations	1,550		
Answered follow-up questionnaire	1,028	or	66.3%
736, or 47.5%, were performed at cesarean section			
137, or 8.8%, were performed at hysterotomy			
68, or 4.4%, were performed post partum			
609, or 39.3%, were performed at gynecologic operation			
Average age, 34 years			
Private 762	White 1347		
Ward 788	Negro 203		

Table V shows the combined totals of the three surveys made in our institution.* The surveys cover a period of twenty-five years. A total of 1,550 patients were operated upon and sterilized by the Pomeroy technique.

TABLE VI. 1924 TO 1949

Total Pomeroy sterilizations	1,550
Total mortality	11, or 0.7%
Causes of Death*:	
Nephritic toxemia	2
Acute myocardial failure	3
Peritonitis (generalized)	2
Pulmonary embolism	1
Lobar pneumonia	1
Miliary tuberculosis	1
Ruptured uterus	1

*None of these deaths occurred in patients upon whom postpartum sterilization was performed.

Table VI shows the causes of death in eleven patients, or 0.7 per cent, of the 1,550 cases reported. One of these deaths was attributed to the operation upon the Fallopian tubes. This death occurred in a patient who had an anteroposterior colpoperineorrhaphy and the peritoneal cavity was opened vaginally only for the purpose of sterilization. This patient succumbed to a spreading peritonitis from an abscess of the right broad ligament which was not diagnosed until rupture had occurred. We therefore feel that entering the peritoneal cavity for the performance of the sterilization was the etiological factor in the development of the broad ligament infection. However, all of the deaths occurred in patients having other procedures concomitantly performed. All of these patients were comparatively poor operative risks or succumbed to conditions over which we had no control. In the entire series of 1,550 cases no major complication such as postoperative bleeding developed following resection of the tubes. In this series there were four failures, or an uncorrected incidence of 0.25 per cent; two failures where to our knowledge the Pomeroy technique was followed explicitly and two other failures in which the technique was not properly executed, give a corrected incidence of failure of 0.12 per cent.

History Summaries of "Failed" Pomeroy Operations

CASE 1.—A white primigravida, aged 30 years, was admitted in March, 1941, because of a serious rheumatic heart disease complicating the pregnancy. Consultation resulted in the decision to terminate the pregnancy, which was accomplished by abdominal hysterotomy at which time a Pomeroy sterilization was performed. She made an uneventful recovery. She was again seen in our Clinic in September of the same year, at which time the uterus was found to be enlarged to about the size of an eight weeks' pregnancy and again decision to terminate the pregnancy was concurred in by the cardiologist. A dilatation and evacuation of the uterus were done at this time. The tissue removed at the operation did not, from a macroscopic standpoint, resemble that of pregnancy but careful examination of the fragments of tissue removed showed that there were chorionic villi present. We assume that this patient was pregnant. Since 1941 she has had no further pregnancies.

CASE 2.—A patient who had a Pomeroy sterilization performed at the time of her second cesarean section made an uneventful recovery but four years later it was reported to us that she had been operated upon in another hospital for an ectopic pregnancy. We were unable to secure the pathology report on the tissue removed following the latter operation.

CASE 3.—This patient had had two previous cesarean sections and at the time of the second section a supposed Pomeroy operation was performed. In reviewing the records the pathology report showed that the tissue sent to the laboratory consisted of two segments of

*A small portion of the 1933 to 1939 series was taken from Delaware County Hospital Obstetrical-Gynecological Service.

Fallopian tube; one segment of Fallopian tube was clearly identified, the other was cut tangentially and showed only serosa and fibromuscular tissue. Microscopically, the lumen of the tube could not be demonstrated. We do not feel that this was a failure of the method because the technique was not properly performed. This patient had a pregnancy subsequent to the supposed Pomeroy operation, at which time a third cesarean section was performed. It was reported that again the tube was resected. The operation was done in another institution. The case demonstrates the importance of sending the excised portions of the Fallopian tubes to the laboratory for microscopic examination. The importance is further demonstrated by the fact that in one of the patients in this series[3] microscopic examination of the segments of the tubes revealed a primary carcinoma, very early of course. This patient had a total hysterectomy and bilateral salpingo-oophorectomy. She has been followed in the Tumor Clinic since 1944 and remains in good condition. We believe this to be the earliest primary carcinoma of the Fallopian tube that has been reported.

CASE 4.—This patient had a cesarean section for cephalopelvic disproportion in November, 1946. She made an uneventful recovery and was discharged from the hospital on the eleventh postoperative day. On March 26, 1948, the patient underwent her second cesarean section and also had performed at that time a bilateral Pomeroy sterilization. She is again pregnant at the present time. We will probably have the opportunity of studying these tubes and may derive some information as to why the operation was a failure. The description of the operation, however, shows that the loops of both Fallopian tubes were clamped before they were ligated or excised. We consider that clamping of the Fallopian tubes in the performance of this operation is one of the most important things to avoid and this may be the reason for its failure.

Summary

1. A consecutive series of 1,550 patients sterilized by the method known as the Pomeroy operation is herewith reported.

2. The over-all incidence of the Pomeroy operation was 2.22 per cent. The incidence in obstetric cases was 1.86 per cent. The incidence in gynecologic cases was 3.17 per cent.

3. There were four failures in this series, or an incidence of 0.25 per cent; two failures where to our knowledge the Pomeroy technique was followed explicitly and two other failures in which the technique was not properly executed. The corrected incidence of failure was 0.12 per cent.

4. The important steps in performing this operation are: (a) to use an absorbable suture since a nonabsorbable suture is likely to cut through the serosa with tuboperitoneal fistula formation; (b) to avoid trauma such as clamping the tube before it is ligated; (c) to see that the tubal loop is made in the middle third of the tube because if it is too close to the involuting uterus it may cause a slipping of the ligature; (d) a loop of salpinx should be excised which is not too large and not too small, as removal of a large loop often disturbs the blood supply to the ovary.

5. The obstetrical morbidity rate among 524 obstetric cases was 22.9 per cent. There were 26.6 per cent of the 214 gynecologic patients who had postoperative febrile reactions.

6. There was one gynecologic death attributed to a vaginal Pomeroy procedure performed in conjunction with a vaginoplasty.

7. Puerperal Pomeroy sterilization operations are completed within one to two hours following normal vaginal deliveries to avoid the period of "probable postpartum hemorrhage" and the period of "probable puerperal infection."

8. One thousand twenty-eight patients, or 66.3 per cent of the 1,550 patients upon whom a Pomeroy sterilization operation was performed, answered "No" to the follow-up questionnaire, "No" indicating no subsequent pregnancy.

Conclusions

We felt that a report of the results of the Pomeroy operation performed in one institution during a quarter century period (from 1924 to 1949), where all operations were done by a comparatively small group of individuals, would allow evaluation of the operation in so far as "simplicity," "safety," and "security" were concerned.

There is no method of tubal steriliaztion known to be 100 per cent successful. However, we feel that the incidence of failure with this technique is less than the incidence of failure of other methods described in the literature.

The use of this operation as a routine and standard procedure in one institution by a closed staff for such a long period of time has given us an opportunity to evaluate our results more accurately. In the light of our findings we will continue the use of the Pomeroy operation.

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ESTROGEN THERAPY OF FUNCTIONAL DYSMENORRHEA: ANALYSIS OF CLINICAL RESULTS*†

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IN A previous publication by some of us[1] regarding functional dysmenorrhea, the correlation of the effect of estrogen therapy on pain, the endometrium, and the basal body temperature was noted. Since that report additional data have accumulated and, as several unexpected results have been noted, we regarded another report to be of interest.

A group of eight patients who supplied faithful clinical data has been selected for this report.

Methods of Study

The effect of the treatment on ovulation was studied by means of basal body temperature graphs. The method of obtaining these graphs has been described elsewhere by one of us.[2] In some few instances endometrial biopsies were obtained also within eighteen hours of the onset of menstrual bleeding. These biopsies were read by one of us (E. C. H.). The effect on pain was decided only from the patients' statements.

Methods of Treatment

Conjugated estrogens (Premarin) were administered orally from day 5 through day 24 of the menstrual cycle, inclusive. In general the plan of treatment was to establish a dose of estrogens which would relieve the pain and which would suppress ovulation. An attempt was made subsequently to reduce the dose until ovulation occurred but no pain was experienced. Finally, an attempt was made to withdraw the medication entirely to determine whether or not the effect would be carried over into further cycles. Daily dosages of conjugated estrogens varied from the equivalent of 0.3125 to that of 3.75 mg. of sodium estrone sulfate.

Presentation of Clinical Data

Pertinent data of these patients are as follows:

Age.—The age at the first visit to this clinic varied from 18 to 30 years. The average age was 21.8 years.

Status.—All of the patients were white. Four were single and four were married.

Parity.—Seven of the patients were nulliparas. The other one was para 2-0-2.

*This study was aided by grants to one of us (E. C. H.) from the Research Council of Duke University and from Ayerst, McKenna & Harrison, Ltd., New York, N. Y.

†Conjugated estrogen (Premarin) used in treatment was supplied by Ayerst, McKenna & Harrison, Ltd., New York, N. Y.

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Age at Menarche.—The age at menarche varied from 11½ to 14 years. The average age at menarche was 12.4 years.

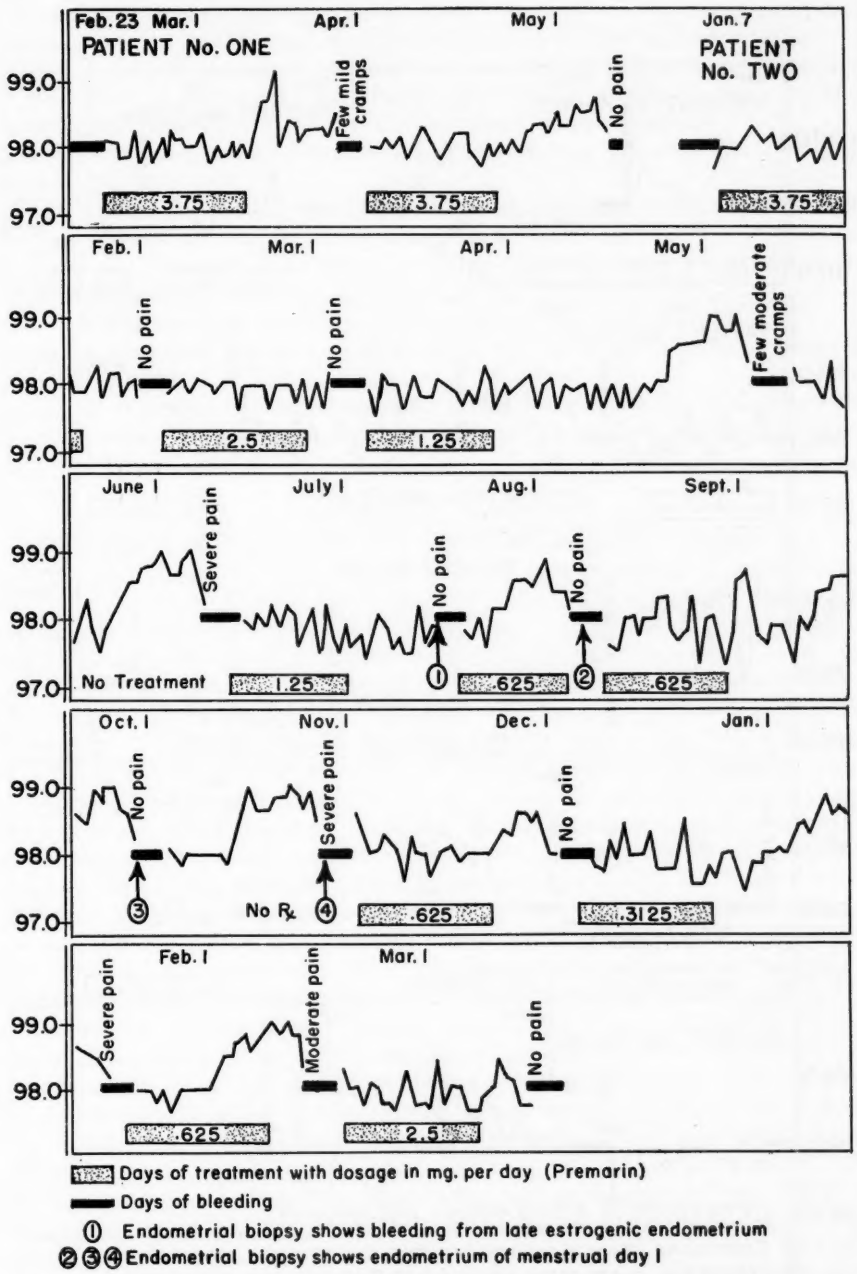

Fig. 1.—Estrogen dosage schedules and clinical responses, including basal temperature graphs and endometrial findings on biopsy of Patients 1 and 2.

Duration of Dysmenorrhea.—Two of the patients had had dysmenorrhea since menarche. Five others had had dysmenorrhea for periods varying from 2 to 6 years with an average duration of 3.6 years. The remaining patient had had dysmenorrhea for 2 years, since the birth of her second child.

Severity of Dysmenorrhea.—Most of the patients complained of severe cramping pain requiring from one to two days of bed rest at the time of their menses. At least two of the patients had required hypodermic injections for relief of pain.

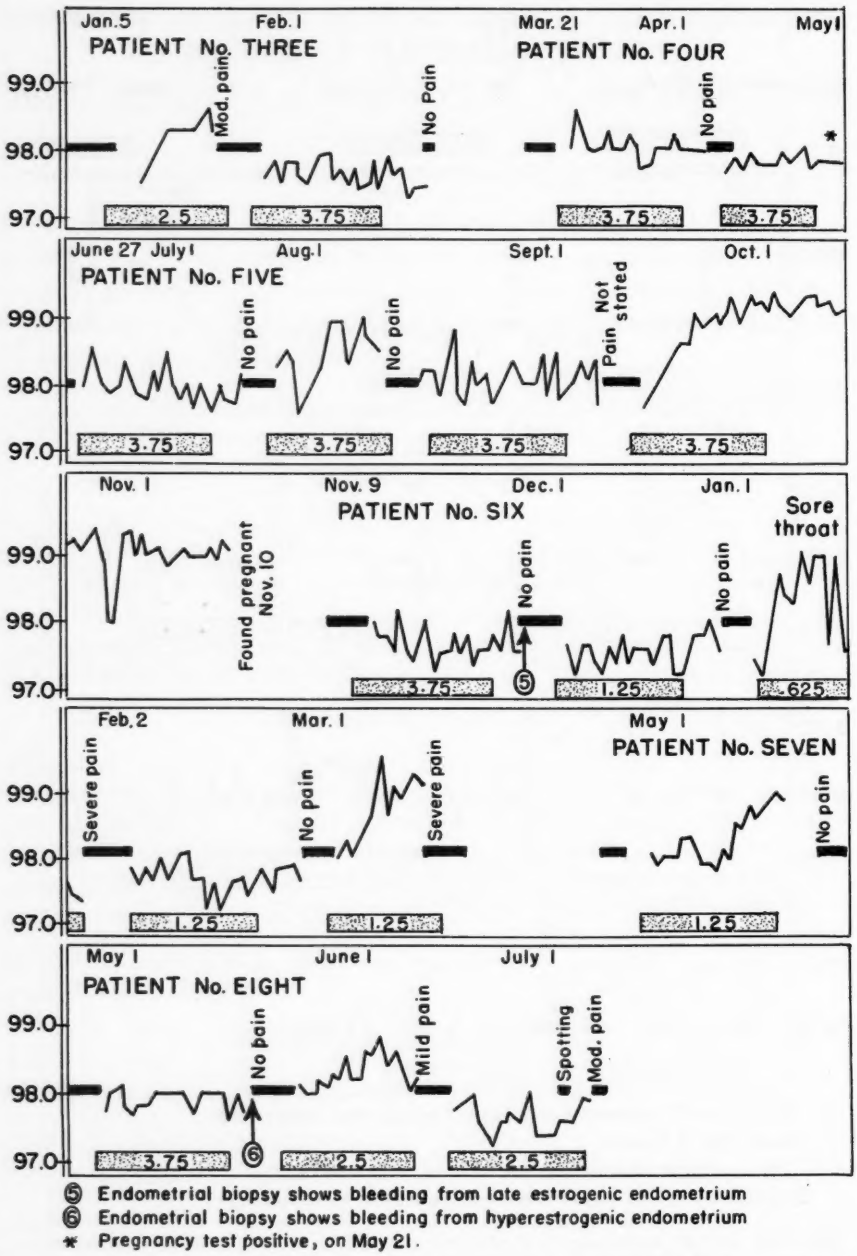

Fig. 2.—Estrogen dosage schedules and clinical responses, including basal temperature graphs and endometrial findings on biopsy of Patients 3, 4, 5, 6, 7 and 8.

Characteristics of the Menstrual Cycle.—These were well within the ranges of normal for all the patients. The interval varied from 25 to 34 days. Patient 2 stated that she had had several cycles of 57 to 58 days' duration in the six

months prior to her first visit here. The duration of flow varied from 3 to 7 days. From 2 to 7 pads per day were required by the various patients.

Associated Clinical Findings.—Patient 1 had albuminuria but no urological disease was found on retrograde pyelograms.

Patient 5 had premenstrual tension and also probably had adnexitis.

Patient 7 stated that her menses became scanty when the dysmenorrhea began. She gave a history of a palpable left lower quadrant mass at the end of her menstrual periods but it could not be found in this hospital.

Possible Psychosomatic Factors.—Patient 6 was an orphan, living in an orphanage.

Patient 8 was studied by the psychiatry service and a diagnosis of anxiety hysteria was made.

Response to Previous Treatment.—Patient 2 had received atropine in this clinic with no relief.

Patient 3 had received nicotinic acid in this clinic with no relief.

Patient 4 had had a cervical dilatation and had worn a stem pessary five years previously with no relief.

Results of Treatment.—The data of treatment schedules and responses including basal body temperature graphs and endometrial findings are presented graphically in Figs. 1 and 2.

Comment

A consideration of these data reveals several interesting things.

Perhaps the most striking finding is that two patients (4 and 5) became pregnant while taking doses of estrogens calculated to suppress ovulation. In fact, in both of these patients ovulation had been suppressed during the month previous to that during which they became pregnant by that same dose of estrogens (3.75 mg. daily for twenty days). This dose, however, had had variable effects in Patient 5: namely, that ovulation had been suppressed twice but permitted once in the cycles before the one during which she became pregnant. Patient 4 took estrogens for only thirteen days of the cycle during which she became pregnant (day 5 through day 17 of the cycle); accordingly, it is possible that she ovulated after she had stopped taking estrogens. Unfortunately she did not continue to take her basal body temperature and the portion of the cycle graphed does not show a rise suggestive of ovulation.

The eight patients were treated during a total of twenty-nine cycles. Two patients became pregnant and the pain was not reported once, with the result that the effect of treatment on pain may be studied in twenty-six cycles. Of course, these figures are too small to be of definite significance but certain tendencies were noted. Thus, whenever any patient received 3.75 mg. of conjugated estrogens daily, pain was entirely absent during the following menstrual period. Lower doses were effective in controlling pain approximately half of the time.

The effect on ovulation is not nearly so apparent. Each of the doses above 0.625 mg. daily suppressed ovulation approximately half of the time. The lower doses, 0.625 mg. and 0.3125 mg., were never successful in suppressing ovulation. It must be emphasized, however, that with the exception of one cycle of one patient, whenever ovulation was suppressed, pain was completely relieved. The one exception occurred in a patient who had an anxiety hysteria. The effect of estrogens on ovulation is quite variable, since a given dose will suppress ovulation in a patient one month and permit it to take place another month. Of course, a given dose varies in its effects on different patients also.

Summary

A review of the treatment of dysmenorrhea with estrogens in eight selected patients is presented. Although the number of observations recorded is not

sufficient to be of definite significance, certain tendencies were noted and the following conclusions seem justified.

1. The effect of estrogens is quite unpredictable since a given dose may suppress ovulation in a patient one month and not do so the next month.

2. In all of the patients 3.75 mg. of conjugated estrogens daily from day 5 through day 24 of the menstrual cycle were effective in completely relieving dysmenorrhea.

3. No such relation between doses of estrogens and the suppression of ovulation was demonstrated. Each of the daily doses greater than 0.625 mg. was successful in suppressing ovulation approximately half of the time.

4. With one dubious exception, whenever ovulation was definitely suppressed, pain was completely relieved.

5. Two unusual results were noted, namely, that two pregnancies occurred while patients were receiving doses of estrogens which had been successful in suppressing ovulation during previous months.

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CHLOROMYCETIN IN THE THERAPY OF GRANULOMA INGUINALE*

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GRANULOMA inguinale, a perplexing problem which has long plagued the South is, at least in Georgia, well on its way to complete eradication. In fact, of the many patients admitted to the wards of the University Hospital in the past ten months, only one was from the city of Augusta. The rapid disappearance of this disease is due primarily to the effectiveness of various antibiotics in therapy. The use of streptomycin,[1] aureomycin,[2] and Chloromycetin[3] has rapidly reduced the number of patients available for study.

Material

Streptomycin was employed in the therapy of 142 patients with granuloma inguinale. A cure rate of 86.6 per cent was obtained with a single course of treatment. The average effective dose was 20 Gm. administered intramuscularly in 1 Gm. doses every six hours for five days. In the nineteen failures the initial dose was inadequate in six, being 10 Gm. or less. Fourteen who failed to obtain a cure following the first course responded successfully to a second course of treatment. There were only five patients who proved to be streptomycin resistant, a failure rate of 3.5 per cent. All of the streptomycin-resistant patients, however, proved responsive to aureomycin therapy. The advantage of streptomycin therapy is the shortness of the period necessary for treatment, i.e., five days. The disadvantage is the need for hospitalization.

Aureomycin has been used in forty-six patients. Intramuscularly, in doses of 250 mg. every four hours for totals of 800 to 1,500 mg., the drug proved ineffective. Orally, this antibiotic proved most efficacious. The lesions in the five streptomycin-resistant patients were healed with oral aureomycin and the lesions in most of the other patients responded readily. Early in our experience with the use of this antibiotic as little as 5 Gm. were used in doses of 250 mg. every four to six hours. The lesions healed superficially but Donovan bodies could be demonstrated deep in the tissues after apparent healing. Breakdown occurred in each instance and the dosage was stepped up so that the average patient received 20 to 30 Gm. in doses of 500 mg. every six hours for ten to fifteen days. In this series the smallest dosage used that effected a cure was 10.8 Gm. and the largest dose required was 70 Gm. In this latter instance the patient had extensive lesions measuring some 300 sq. cm. in size. The patient proved resistant to three courses of streptomycin in which a total of 158 Gm. was used. Although complete healing was obtained with 50 Gm. of aureomycin, another 20 Gm. were added as insurance against a relapse. Though 20 to 30 Gm. of the drug appear to be sufficient for the average case, it was found that patients with extensive lesions or with slowly responsive lesions required from 40 to 70 Gm. In several instances, healing was incomplete after one course of

*Aided by grants from the State of Georgia Department of Public Health and the United States Public Health Service.

therapy and a second course was given. Only two relapses have thus far been observed in patients who had healed after receiving 20 Gm. or more of the drug. In these instances successful responses were obtained on re-treatment. The patients in this series have now been under observation from one to ten months. Half of them have been followed for at least five months. Toxic reactions such as nausea, vomiting, and diarrhea have been encountered in several of the patients with 500 mg. dosage, and much more frequently when the dosage was stepped up to 1 Gm. every six hours.

A. *B.*

Fig. 1 (Case 1).—*A*, Before treatment with Chloromycetin. *B*, After 20 Gm. of Chloromycetin administered in dosage of 500 mg. every six hours for ten days.

Chloromycetin is the antibiotic now under scrutiny. Between March 18, 1949, and Sept. 16, 1949, therapy with this antibiotic was employed in twenty-three women patients. The dosage at first was chosen arbitrarily at 20 Gm. One-half gram every six hours was administered over a period of ten days to four patients. The response was striking. One gram was administered every six hours over a period of five days to the four other patients. The results appeared equally good. In each group there was one case with incomplete healing and a second course of therapy was necessary before complete healing occurred. Two patients were treated with 70 and 40 Gm., respectively. It appeared that that dosage was required for complete healing in patients with extensive lesions; hence the variance in dosage. Most of these patients have now been followed for four to six months. The results are most promising. Untoward effects have not been noted. Two relapses occurred and these patients responded to a second course of Chloromycetin. Donovan bodies disappear from the lesions more rapidly than with aureomycin or streptomycin. The advantages of its use are that it may be administered on an outpatient basis and that it is not toxic. When administered to hospitalized patients the disadvantage is the length of time required for treatment, i.e., 10 to 20 days. The following case histories illustrate the excellent results:

Case 1.—L. M., a Negro woman, aged 62 years, was admitted on March 10, 1949, with lesions involving the perineum and perianal region present for four years. There had been no response to previous antimonial therapy. She also had a rectal stricture. The complement fixation test for lymphogranuloma venereum was positive in a dilution of 1:240

although the Frei test was negative. Donovan bodies were found in smears from the lesions. She received 20 Gm. of Chloromycetin as 500 mg. four times daily for ten days. The lesions regressed rapidly and Donovan bodies disappeared within seventy-two hours. The lesions were 90 per cent healed upon completion of therapy. She has been observed at monthly intervals since and the lesions have remained healed (Fig. 1).

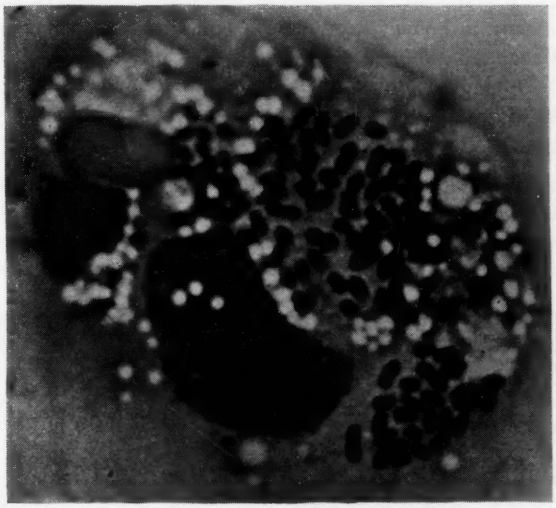
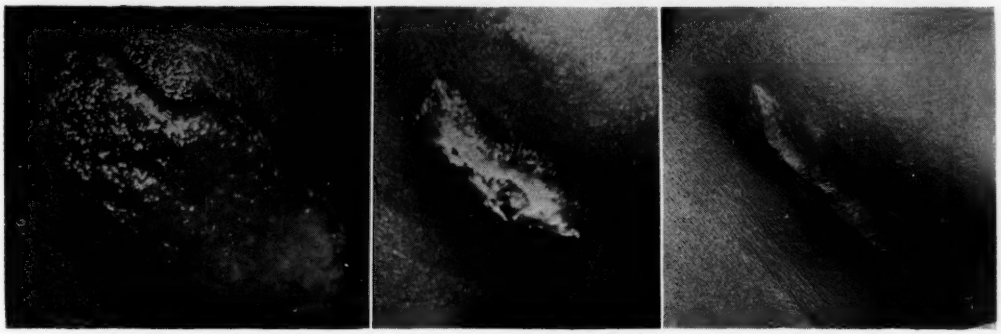


Fig. 2 (Case 2).—Donovan bodies.



A. *B.* *C.*

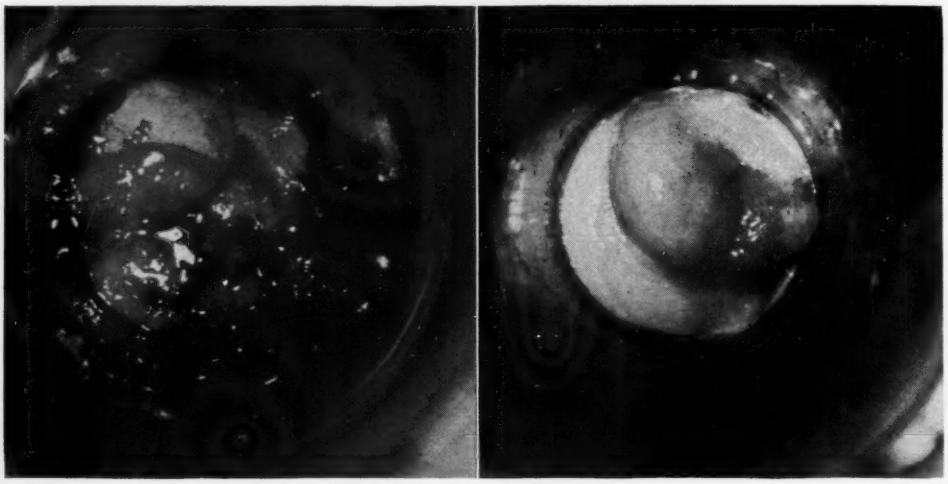
Fig. 3 (Case 2).—*A*, Before treatment with Chloromycetin. *B*, After first course of 20 Gm. of Chloromycetin over a period of ten days, showing 80 per cent improvement in lesion. *C*, After a second similar course of therapy healing was completed.

CASE 2.—C. L. W., a 23-year-old Negro woman, who was placed on treatment March 15, 1949, presented a large granulomatous lesion on the right cheek covering 30 sq. cm. in area, in addition to lesions of similar size on the vulva and perineum which had been present for two years. The vulvar lesions had previously healed under antimonial therapy but recurred. Donovan bodies were plentiful in smears from both areas (Fig. 2). These disappeared within seventy-two hours after the institution of Chloromycetin therapy, 20 Gm. in ten days. The vulval lesions were entirely healed and the lesion on the right cheek was 80 per cent healed by the completion of treatment (Fig. 3, *A* and *B*). However, the extragenital lesion did not completely heal and Donovan bodies could again be demonstrated in smears from this lesion. Another course of 20 Gm. was administered. Healing occurred and 10 Gm. more were added for good measure. The patient remains well (Fig. 3, *C*).

CASE 3.—E. P., a 17-year-old Negro woman, presented a lesion of granuloma inguinale of the vulva which had been present for eight months. Therapy with Chloromycetin was begun on April 18, 1949. She received 20 Gm. in ten days and the lesions were 90 per cent healed upon completion of therapy. The patient has been seen for follow-up and the lesions have remained well.

CASE 4.—C. L., a 22-year-old Negro woman, presented lesions of the vulva of five weeks' duration in which Donovan bodies were demonstrated. She was placed on therapy with Chloromycetin on March 25, 1949, and received 20 Gm. in five days. Healing was only 50 per cent complete and a second course of 20 Gm. over ten days was given. She has been seen at monthly intervals and has remained well.

CASE 5.—D. W., a 35-year-old Negro woman, seen April 4, 1949, presented a small granulomatous lesion of the lower abdomen and several small similar lesions of the vaginal wall. Donovan bodies were found in these lesions and Chloromycetin was given as 1 Gm. four times daily for a total of 20 Gm. in five days. Donovan bodies could not be demonstrated in seventy-two hours and the lesions were healed at the completion of therapy.



A. *B.*

Fig. 4 (Case 6).—Granuloma inguinale of the cervix. *A*, Before treatment with Chloromycetin. *B*, After 40 Gm. of Chloromycetin over a period of twenty days.

CASE 6.—L. S., a 29-year-old Negro woman, seen April 15, 1949, presented granulomatous involvement of most of the cervix together with roentgen evidence of granuloma inguinale of the sacrum as represented by cystic areas. Bacitracin in suppository form was tried without success. Chloromycetin was then given and Donovan bodies could not be demonstrated after seventy-two hours. The cervix was entirely healed upon completion of 40 Gm. in twenty days. The tenderness and swelling over the sacrum decreased rapidly and the cystic areas had healed within one week. She has been observed at monthly intervals and has remained well (Fig. 4, *A* and *B*).

Other antibiotics have been tried. Penicillin proved ineffective, tyrothricin used locally and bacitracin used in the form of suppositories proved valueless. In this connection, it may be stated that streptomycin suppositories were used in seven cases and proved effective in four.

Conclusions

1. Twenty-three women patients with granuloma inguinale were effectively treated with Chloromycetin. Six case histories are detailed in the text.

2. The total dosages necessary for cure were 20 Gm. in six cases, 40 Gm. in two, 50 Gm. in one, and 70 Gm. in another. From our experience it appears that the ideal dosage is 500 mg. every six hours for ten to twenty days. If healing is incomplete or the lesions are extensive it is advisable to continue Chloromycetin until 50 to 70 Gm. are given.

3. Donovan bodies, in most instances, disappeared from the lesions in two to four days after therapy was begun.

4. Untoward effects were not observed.

5. One hundred forty-two patients with granuloma inguinale were treated with streptomycin with excellent results. Five patients proved to be streptomycin resistant. Twenty grams intramuscularly in dosages of 1 Gm. every six hours over a period of five days seemed adequate in most instances.

6. Aureomycin was used in forty-six patients. The effective dose range varied from 10.8 to 70 Gm. On the average the dosage used was 20 to 30 Gm. Untoward results were nausea, vomiting, and occasionally diarrhea. Aureomycin given intramuscularly was not effective in the dosage employed.

7. The antibiotics Chloromycetin, aureomycin, and streptomycin have proved most effective agents in reducing the incidence of granuloma inguinale in Georgia.

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POLIOMYELITIS IN PREGNANCY

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THE occurrence of poliomyelitis in association with pregnancy has been a subject of special interest to us over the past several years. It has been our clinical impression that in recent years we have seen these cases in a number which would suggest more than a chance distribution of the disease in pregnant women.

An analytical consideration of this subject is important because it has bearing not only on the current concepts of susceptibility to the virus of poliomyelitis but also on the prognosis of fetal survival and morbidity as well as the related obstetrical problems.

In 1945, Fox and Sennett[1] and, in 1947, Fox and Waisman[2] reviewed this subject and added to the literature a total of eighteen cases of poliomyelitis complicating pregnancy. At the time of the 1947 study, a survey of the literature revealed a total of 175 reported cases. Since these publications appeared, several articles of importance have been written dealing with the problems of poliomyelitis in pregnancy, further substantiating the impressions previously presented that the occurrence of poliomyelitis in the pregnant woman is no rarity in this country though reports from England show that the incidence there is comparatively low.[3] While the high frequency of this mishap in our community has been alarming to us and has perhaps colored our impression of the importance of the problem, we are not unmindful of the capricious nature of poliomyelitis nor of the fact that it is a disease which varies from year to year in its intensity, distribution, and general characteristics.

In 1941, Aycock,[4] who has repeatedly emphasized the importance of the role of variable susceptibility, reviewed this subject and estimated that one might anticipate an incidence of one case of poliomyelitis in 50,000 pregnancies. He found an actual increase in the incidence over the anticipated frequency and pointed out that the endocrine changes occurring in pregnancy might be important factors in the frequency with which the pregnant woman contracts poliomyelitis. Shaefer and Shaw[5] have recently stated that aside from the purely endocrine changes, the stresses and strains of pregnancy may predispose toward the susceptibility to poliomyelitis. This fits in well with the fatigue factor which has been repeatedly shown to have an adverse effect on the animal or human being infected with the poliomyelitis virus.

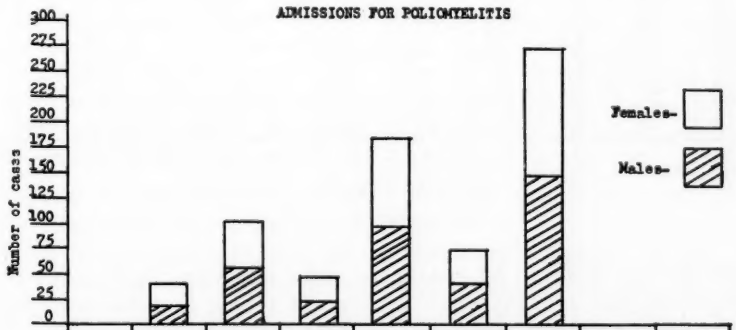
In the past few years other investigators have become increasingly interested in this and related problems. In a report by Setälä,[6] the author emphasizes the extension of the disease into the older age groups with an accompanying greater incidence in pregnancy. In contrast, Dauer,[7] in his careful analysis of the age distribution of poliomyelitis indicates that the extension of the disease into the older age groups is more apparent than real and is probably accounted for by a change in the age composition of the population and by an increase in the number of cases reported per death. Horton and Rubenstein,[8] in their

analysis of poliomyelitis in Massachusetts, have arrived at a similar conclusion. Setälä[6] further observes that the number of pregnant women with the disease varies from year to year, suggesting an alteration in predisposition to poliomyelitis in this group. Other reports have appeared within the past five years which give support to the belief that poliomyelitis in pregnancy is assuming increasing frequency and importance. Davis and Silverstein,[9] Baker and Baker,[10] have aptly pointed to this trend.

With the recent appreciation that congenital malformations are in some instances related to rubella occurring in the first trimester of pregnancy, there has ensued a search for evidence of similar effects from other virus diseases of the gravid woman on her unborn child. Poliomyelitis is under consideration in this regard. Because this disease seems to have a relative affinity for the pregnant woman, the opportunity to study the effect of the disease on the fetus has presented itself in various epidemics. This report deals in part with such a study and brings to date our own experience with this problem, comparing it with the experience of others in hope that it may prove informative to those who are interested in the study of poliomyelitis and to those who may meet the problem in the practice of obstetrics.

Incidence of Poliomyelitis in Pregnancy

From 1943 through 1948, a total of thirty-three women in whom poliomyelitis was associated with pregnancy were admitted to South View Isolation Hospital of the Milwaukee Health Department. We have attempted to study these cases from several aspects: first, to determine if our series represented a higher incidence of poliomyelitis in pregnant as compared with nonpregnant women of childbearing age; second, to determine what effect poliomyelitis had on the course of pregnancy; and third, to determine what effect poliomyelitis might have on the surviving infants.



	1943	1944	1945	1946	1947	1948	Total	%
CASES	43	106	47	181	72	268	717	100
Females	22	47	22	84	32	122	329	46
Males	21	59	25	97	40	146	388	54

Fig. 1.

Over the course of this six-year period a total of 717 patients with verified cases of poliomyelitis have been admitted to this fever hospital in the numbers and sex ratios indicated in Fig. 1. The ratio of males to females did not vary significantly from year to year. Of the total of 717 cases, 329, or 46 per cent, were females. A further breakdown of this group of females (Table I) reveals that seventy-four patients were in the childbearing years of 18 to 45. Fifty-six of these seventy-four patients were married women, and twenty-eight of these

were pregnant. Two were immediately post partum, and one was four days post abortion at the time of admission. In addition, there were two unmarried but pregnant women admitted. This makes a total of thirty-three cases of poliomyelitis occurring in conjunction with pregnancy which have been treated over the past six years. Of all the married women of childbearing age who had poliomyelitis, 57 per cent were pregnant. Horstmann[11] has reported a 32 per cent incidence of poliomyelitis in pregnancy in the 1944 epidemic in Copenhagen.

In breaking down this series of 717 cases into age and sex groups as shown in Fig. 2, it is of interest that before the age of 18 years the percentage of males with clinically recognizable poliomyelitis is greater than that of females. Why this difference occurred in our series of cases is not entirely clear, but since the greatest number of cases occurred in the 5- to 9-year-old age group in both sexes, and since it has been demonstrated repeatedly that fatigue is an important factor in the occurrence of recognizable poliomyelitis,[12, 13] it is likely that this sex difference may result from the more vigorous activity of the male child and his resultant greater fatigue.

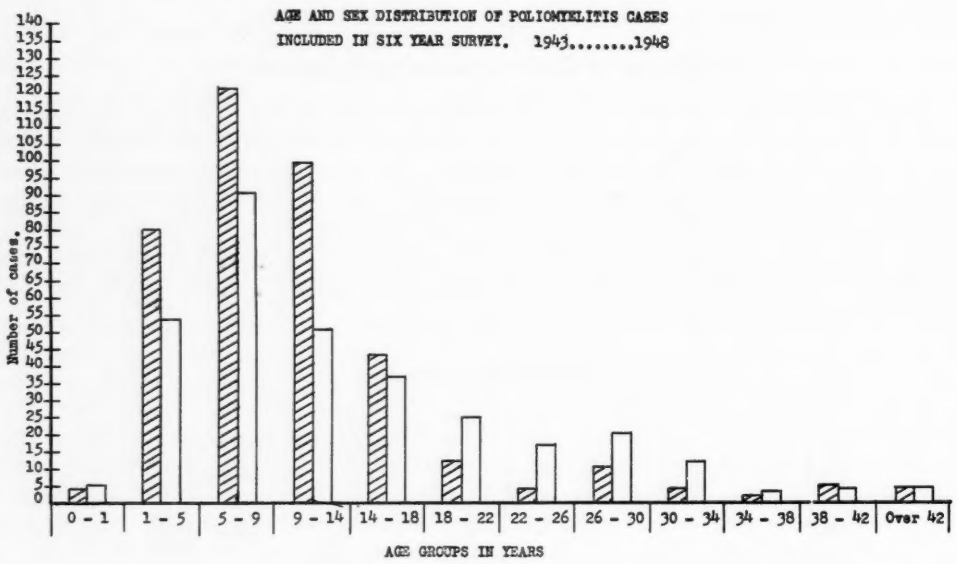


Fig. 2.

In the age group of 18 to 46 years, the sex ratios tend to reverse themselves, with forty-one men and seventy-four women, of whom forty-one were not pregnant. Thus the thirty-three pregnant women are entirely responsible for the reversal of the sex ratio seen in this adult group. This further suggests that pregnancy increases the susceptibility of the female to poliomyelitis while the nonpregnant adult female is no more susceptible to the disease than the adult male.

The incidence of pregnancy in reported poliomyelitis epidemics has been variable, but it has been previously stated[14, 15] that the incidence of the disease is twice as great in pregnant as in nonpregnant women of the same age group. Our series indicates a similar incidence of pregnant poliomyelitis victims: 44.5 per cent of all the women in the period of fertility were pregnant and of the married women who are admitted 57 per cent were pregnant.

Whether or not the chronic fatigue or the endocrine changes of pregnancy are responsible for this difference in susceptibility is an unsettled problem and one which seems worthy of further consideration.

We feel that this 57 per cent incidence of pregnancy in the married women of our series is in excess of the proportion of pregnant married women in the population of this community. Taylor and Simmons[14] estimated that 11.7 per cent of the women of Colorado between the ages of 17 and 40 were pregnant on any given day during the epidemic of 1946 in that state.

TABLE I. POLIOMYELITIS IN WOMEN, 1943-1948

Total women admitted	329
Total women, 18 to 45 years	74
Total married women, 18 to 45 years	56
Total married pregnant women	31
Total unmarried pregnant women	2
Per cent married women who were pregnant	57

Effects of Poliomyelitis on the Course of Pregnancy

There were four deaths among the thirty-three patients whose pregnancies were complicated by poliomyelitis, or a mortality rate of 12.1 per cent. Two of these died after having given birth to normal infants; one, nine days, and the other thirteen days post partum. Of the other two, one was three months and the other four and one-half months pregnant at the time of death.

Seven patients, or 21.2 per cent, aborted. Since the over-all incidence of abortion in pregnancy has been estimated at 24 per cent,[15] it would seem that the occurrence of abortion in the group of patients under study is not in excess of that which might normally have been anticipated had the women not contracted poliomyelitis; however, such a direct comparison is not entirely applicable for this selected group. Gifford and Hullinghorst[16] have reported a fetal death rate of 26 per cent in a survey analysis of 170 cases of poliomyelitis in pregnancy. In our group of seven patients who aborted, one was 1 month pregnant, one was 2 months, two were 3 months, two were 3½ months, and one was 5½ months pregnant. Thus all the abortions occurred within the first two trimesters: four in the first and three in the second. One of these patients aborted four days prior to the acute onset of her illness. The other patients aborted during their periods of isolation or very shortly thereafter. This would seem to suggest a relationship between the acute illness and the abortion.

The severity of the paralytic manifestations of the disease seemed to bear no relationship to the tendency to abort, a few of the most severely paralyzed mothers having carried their babies to full term.

None of the patients in this series developed straight bulbar paralysis, in spite of an incidence of 18.2 per cent of such cases with a 48.2 per cent mortality occurring in the 1948 epidemic in this community. Although a few of the pregnancy cases developed cranial nerve signs, the initial evidence of the disease appeared first as manifestations of cord involvement. Taylor and Simmons[14] reported four presumably straight bulbar cases in their series of twenty-five pregnancies, which would indicate that this single manifestation of the disease does occur in pregnant women. The absence of such cases in our series has given us cause to wonder regarding the common portal of entrance of the virus in pregnant women.

From an analysis of the cases included in this series, it was found that the ages of these patients varied considerably within the period of fertility. The history of previous pregnancies seemed to be of no significance. In a follow-up study, fifteen of the thirty-three patients related no subjective evidence of residual disability from the disease. Fourteen patients related varying degrees of residual paralysis or paresis resulting from their acute disease.

Effect of Poliomyelitis on the Infant

A follow-up of the twenty-nine living patients and their offspring revealed that twenty normal babies of average birth weight were born to the surviving mothers. Two more normal babies were born to mothers who subsequently died of poliomyelitis. Two infant deaths occurred in our series. One of these was the result of erythroblastosis and the other resulted from cord hemorrhage which presumably occurred during labor. Seven patients aborted and two could not be traced. Two of the babies were delivered by cesarean section. In both of these cases the mothers were severely affected and both had flaccid abdominal muscles. No complications of pregnancy other than poliomyelitis were reported except in one patient who had syphilis. The baby of this mother was normal, however.

In this study we could find no evidence to suggest that poliomyelitis affecting the pregnant woman leaves any stigma on the fetus if it survives the acute illness of the mother. Significant congenital malformations are thought to occur in the relatively early phases of pregnancy while the embryo is undergoing its complex structural development. We might logically anticipate that if poliomyelitis were to affect the infant in utero, it would most likely become manifest in those infants whose mothers contracted the disease early in pregnancy, particularly within the first three months. In our series, eight of the women admitted to the hospital were three months pregnant or less and subsequently delivered normal infants. Of these, four were less than two months, two were two and one-half months, and two were three months pregnant at the time of admission.

Four other women who were pregnant three months or less aborted in association with their poliomyelitis attacks. We did not have the opportunity to examine the products of conception in these cases in order to search for congenital malformations.

In the eight cases of early pregnancy which we have been able to study, no congenital malformations resulting from poliomyelitis were observed. In this respect our study is in agreement with previous impressions gained through clinical study and animal experimentation. One cannot help but be impressed by the fact that this most deadly and crippling disease leaves no apparent mark on the surviving babies while the relatively benign virus infection of rubella leaves in its wake infants who are blind, deaf, or in many other ways deformed.

Conclusions

From a study of 717 patients with poliomyelitis admitted to the South View Hospital during the past six years, a total of thirty-three patients were found in whom pregnancy coexisted with this disease. These patients were studied with regard to the incidence of poliomyelitis in pregnancy, the effect of the disease on the course of pregnancy, and the effect of the disease upon the surviving infants born to these patients.

This study revealed that 57 per cent of the married women of childbearing age admitted for poliomyelitis were pregnant. This is considered well in excess of the percentage of pregnant married women in the random population and would seem to indicate an increased susceptibility of the pregnant woman to clinically recognizable poliomyelitis.

Of the thirty-three cases of poliomyelitis in pregnancy herein presented, the incidence of abortion was 21.2 per cent, which, while not unusually high for a group of pregnant women, was nevertheless closely associated with the episodes of acute illness. Four patients died, making the mortality rate 12.1

per cent for the group. Labor and delivery were complicated as a result of poliomyelitis in only two patients and these were delivered successfully by cesarean section.

A follow-up study of this group of women revealed that twenty-two normal babies of average birth weight were born. There were two infant deaths: one stillbirth resulting from cord hemorrhage, and the other from erythroblastosis. There is no evidence to indicate that poliomyelitis in the mother left any stigma on the surviving infants.

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SERUM POLYSACCHARIDE LEVELS IN PREGNANCY, PARTURITION, AND THE POSTPARTUM STATE*

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FEW investigations have been published concerning the effect of the pregnant and postpartum state on the serum polysaccharide level in women. West and Clarke[1] reported serum glucosamine values for two pregnant and ten postpartum patients. Novak and Lustig[2] recently reported data on the carbohydrate content of serum protein, of albumin, and of globulin using the orcinol method. In connection with our studies of the relationship of tissue polysaccharides to malignancy we have surveyed the effect of pregnancy and parturition on the serum polysaccharide level.

Experimental

Nonglucosamine polysaccharide was determined by the tryptophane method as previously described.[3] Glucosamine was determined by the acetylacetone method or by the biuret method of Weichselbaum[4] standardized by the Micro-Kjeldahl method. Albumin, α-globulin, and combined β- and γ-globulin were determined by sodium sulfate fractionation as described by Milne.[5] The γ-globulin was determined by the method of Jager and Nickerson[6]; and by 33 per cent saturated ammonium sulfate precipitation β-globulin was found by difference. Nonglucosamine polysaccharide was determined on the albumin and albumin + α-globulin after precipitation with absolute ethanol from the sodium sulfate solutions. Nonglucosamine polysaccharide was determined on the γ-globulin fraction after dissolving the precipitate resulting from the ammonium sulfate precipitation in 0.9 per cent saline and reprecipitating with absolute ethanol. The estimation of the nonglucosamine polysaccharide associated with the α-globulin and β-globulin was then obtained by difference.

Normal women in early pregnancy were selected from the obstetric clinic after a careful survey of charts and examination of the patient to rule out complications. Blood samples were taken approximately once a month until parturition. In one case (48040 A) the study was continued post partum.

For the parturition studies, women were selected as they came to the obstetric clinic for delivery. Blood samples were taken before and immediately after parturition, and at various times post partum. A sample of fetal blood was obtained by needle from the umbilical vein of the cord on the placental side, immediately after clamping and cutting of the cord.

Results

Data obtained on twenty-nine patients in pregnancy, thirteen of whom were primigravidas, are presented in Table I. No appreciable difference was found between the primigravidas and the multigravidas. Data on the albu-

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min, α-globulin, β-globulin, and γ-globulin content and the polysaccharide of these fractions in the sera of eight of the same patients are summarized together with comparable data from fifteen nonpregnant subjects in Table II. The data for pregnancies were compared statistically with those of nonpregnant women using the following formula from Rider.

$$t = \frac{X_1 - X_2}{\left(\frac{N_1 + N_2}{N_1 + N_2 - 2}\right)^{1/2} \left(\frac{N_1 S_1^2 + N_2 S_2^2}{N_1 N_2}\right)^{1/2}}$$

X_1 and X_2 are the averages of the respective groups, N_1 and N_2 are the number of individuals in the respective groups, and S_1^2 and S_2^2 are the variances of the respective groups. As shown by this table the total protein and the albumin were decreased significantly while the α-, β-, and γ-globulins were all elevated significantly in pregnancy. Further, the total serum polysaccharide and the albumin polysaccharide are elevated significantly when they are expressed as a percentage of their respective protein moieties. On the other hand, none of the globulin fractions show an increase in polysaccharide content. The change in the nonglucosamine polysaccharide levels in pregnancy is made clearer in Table III in which the polysaccharide content of each protein fraction is calculated from the amount of the fraction present

TABLE I. NONGLUCOSAMINE POLYSACCHARIDE, GLUCOSAMIDE, AND TOTAL PROTEIN CONTENT OF SERA IN LATE PREGNANCY

SUBJECT NUMBER	NO. OF MONTHS PREGNANT	AGE IN YEARS	TIMES PREGNANT	NONGLUCOSAMINE POLYSACCHARIDE		GLUCOSAMINE	SERUM PROTEIN
				MG. PER CENT	PER CENT OF PROTEIN		
46066 A	10	24	4	148	2.34	81	6.31
146-460	10	33	6	149	2.32	84	6.44
136-881	10	25	5	133	2.26	82	5.88
146-441	10	44	2	167	2.49	90	6.70
48040 A	10	30	8	158	2.37	96	6.70
146-683	10	30	3	152	2.32	86	6.57
146-760	10	30	3	174	2.63	82	6.63
137-251	10	22	3	155	2.33	82	6.65
147-475	10	28	3	191	2.59	100	7.37
59468 A	9.5	23	4	142	2.56	75	5.56
137024	8	38	12	162	2.38	90	6.81
144-849	8.5	27	3	131	2.32	72	5.66
59759 A	9	24	2	137	2.35	68	5.86
142-394	9.5	22	5	142	2.34	92	6.06
142-941	9.5	39	6	123	2.41	81	5.10
153-191	9.5	38	5	142	2.63	66	5.40
148-241	9	20	1	141	1.96	88	7.19
55027 A	10	16	1	122	2.26	63	5.41
54-341 A	9	19	1	156	2.55	88	6.11
146-485	10	23	1	172	2.82	81	6.10
146-725	10	20	1	150	2.46	86	6.10
56532 A	8	24	1	157	2.53	82	6.20
59772 A	9.5	19	1	162	2.62	82	6.20
56528 A	9.5	17	1	152	2.46	79	6.18
57000	9	18	1	120	2.12	79	5.65
58922 A	8.5	13	1	160	2.61	92	6.14
57272 A	8	16	1	158	2.49	87	6.35
145-662	10	17	1	167	2.57	112	6.50
59-470 A	8.5	14	1	162	2.58	83	6.28
Average primigravida				152	2.46	85	6.19
Average multigravida				150	2.42	83	6.23
Average nonpregnant				111	1.59	67	6.99

in serum of the average pregnant patient and the average polysaccharide content of the respective normal fraction. It is apparent from this table that some of the increase in polysaccharide in pregnancy is due to the increase in serum globulin which does not change in polysaccharide content. A large portion of the increase, however, is due to a qualitative change of the serum albumin, that is, an increase in the polysaccharide content of this fraction. Although there is a decrease in albumin content, as measured by nitrogen determination, the polysaccharide content of this fraction actually increases. As indicated by Table I the glucosamine polysaccharide in the sera from pregnant subjects was also elevated significantly, the t value for the comparison with normal subjects being 7.91.

TABLE II. SERUM PROTEIN AND POLYSACCHARIDE DISTRIBUTION IN PREGNANT AND NONPREGNANT SUBJECTS

	AVERAGE RESULTS		COEFFICIENT OF VARIATION		
	PREGNANT	NONPREGNANT	PREGNANT	NONPREGNANT	t-VALUE
Protein Distribution.—					
Albumin*	53	67	0.096	0.047	7.92‡
α-globulin*	10	8	0.185	0.164	2.91‡
β-globulin*	19	10	0.185	0.213	7.64‡
γ-globulin*	18	15	0.149	0.124	3.24‡
Polysaccharide Associated with:†					
T. Protein	2.46	1.59	0.075	0.104	13.46‡
albumin	1.29	0.76	0.155	0.173	7.39‡
α-globulin	3.58	3.23	0.340	0.305	0.72
β-globulin	5.07	5.94	0.150	0.296	1.28
γ-globulin	2.54	2.31	0.094	0.162	1.55

*Expressed as percentage of the total serum protein.

†Expressed as a percentage of the protein moiety, i.e., albumin polysaccharide, albumin, etc.

‡Significant at the 1 per cent level of significance.

TABLE III. COMPARISON OF ACTUAL POLYSACCHARIDE DISTRIBUTION IN PREGNANT SUBJECTS WITH THAT CALCULATED FROM NORMAL VALUES

	AVERAGE PER CENT POLYSACCHARIDE IN NORMAL PERSONS	AVERAGE PER CENT PROTEIN FOUND IN PREGNANCY	CALCULATED POLYSACCHARIDE MG. PER CENT	ACTUAL POLYSACCHARIDE MG. PER CENT
Albumin	0.76	3.22	24	42
α-globulin	3.23	0.62	20	22
β-globulin	5.94	1.08	64	60
γ-globulin	2.31	1.10	25	26
Total			133	150

In order to determine the actual time of elevation of the serum polysaccharide in pregnancy, serial determinations were made on six patients. Typical data obtained are present in Table IV. With only one exception, the serum polysaccharide expressed as percentage of the protein was found to be noticeably elevated after the sixth or seventh month. In four cases the elevated polysaccharide level declined slightly just before delivery. The average results are presented graphically in Fig. 1.

Parturition and postpartum studies were made on seven cases, one of which is recorded in Table V; the average results are graphically presented in Fig. 2. In every case the cord blood contained considerably less serum polysaccharide than the corresponding maternal blood. Cord blood from one

syphilitic patient contained more polysaccharide than did the normal cord bloods. Data on parturient and postpartum serum polysaccharides are graphically summarized in Fig. 2. In all but one case lactation occurred; results in this case were essentially the same as in others. In some cases the serum polysaccharide level was elevated soon after parturition. In other cases the polysaccharide decreased temporarily after delivery and after sev-

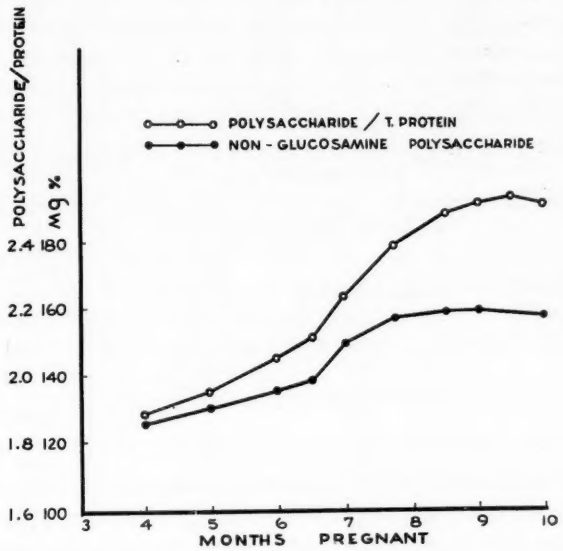

Fig. 1.—The serum polysaccharide level in pregnancy. Average of six cases.

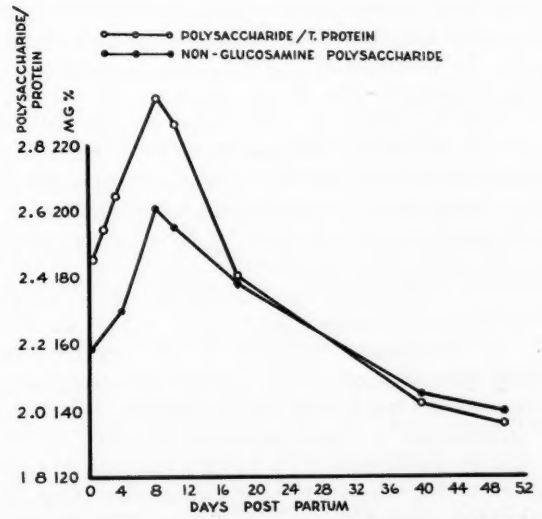

Fig. 2.—The serum polysaccharide level after parturition. Average of seven cases.

eral days increased again. In all cases, however, the polysaccharide level reached its maximum between six and ten days following parturition. The serum polysaccharide then declined slowly but was still above the normal forty-five to fifty days after parturition.

TABLE IV. NONGLUCOSAMINE POLYSACCHARIDE AND GLUCOSAMINE CONTENT OF SERA DURING PREGNANCY

NO. MONTHS PREGNANT	NONGLUCOSAMINE POLYSACCHARIDE		GLUCOSAMINE MG. PER CENT	SERUM PROTEIN PER CENT
	MG. PER CENT	PER CENT PROTEIN		
4	114	1.64	72	6.81
5.5	123	1.83	77	6.71
6	132	2.06	80	6.70
7	144	2.39	92	6.65
8.5	145	2.37	94	6.13
9	151	2.45	92	6.16
9.5	158	2.38	95	6.63
10	158	2.37	96	6.70

TABLE V. NONGLUCOSAMINE POLYSACCHARIDE AND GLUCOSAMINE CONTENT OF SERA FOLLOWING PARTURITION

TIME RELATIVE TO PARTURITION	NONGLUCOSAMINE POLYSACCHARIDE		GLUCOSAMINE MG. PER CENT	SERUM PROTEIN PER CENT
	MG. PER CENT	PER CENT PROTEIN		
40 Minutes before	149	2.32	84	6.44
0.7 Days after	144	2.36	82	6.10
1.5 Days after	154	2.40	88	6.42
3.6 Days after	173	2.72	97	6.36
5.7 Days after	176	2.84	95	6.20
9.0 Days after	188	2.88	98	6.52
20 Days after	157	2.35	80	6.68
30 Days after	135	1.90	73	7.10
53 Days after	137	1.90	75	7.22
Cord Blood	97	1.51	54	6.40

Comment

Data procured in this study indicate that serum polysaccharide is significantly elevated in late pregnancy. This finding is somewhat contrary to the data of Novak and Lustig[2] who reported a nonsignificant elevation of serum polysaccharide in pregnancy. However, it should be noted that these investigators averaged the results from patients in all stages of pregnancy. Novak and Lustig[2] also reported an elevation of the albumin polysaccharide and a depression of the globulin polysaccharide. Our data are in agreement with the former conclusion, but not the latter. Our data indicate no change in pregnancy of the globulin polysaccharide expressed as a percentage of the globulin. The discrepancies may be due to the difference in methods used to precipitate the protein from the polysaccharide determination and to the difference in methods for quantitative estimation of the polysaccharide. In agreement with Novak and Lustig, and with other investigators, we found the serum protein of pregnant women to be significantly lowered, with restoration following parturition. Elevation of the serum polysaccharide level also occurs in cancer, arthritis, tuberculosis, prostatic hyperplasia, nephritis, and many infections.[7] The elevation in some of these conditions has been attributed to tissue destruction.[9] In the case of pregnancy, however, especially in the later months when the maximum elevation occurs, it is difficult to explain polysaccharide elevation on this basis. The authors have previously suggested that the elevation in certain conditions might be correlated with tissue repair or proliferation. In pregnancy one might also correlate the elevation of serum polysaccharide with the growth process, of either the fetus or the placenta.

As the cord blood was always found to contain considerably less polysaccharide than the maternal blood, it appears unlikely that the elevation of

serum polysaccharide of the maternal blood is due to production of excessive amounts of polysaccharide-rich proteins by the fetus. The serum polysaccharide in the cord blood in one case in which the mother was syphilitic was much higher than that of any of the normal subjects. This may be due to a change in placental permeability. Further studies are necessary to establish the relationship of the fetal polysaccharide level to that of the mother.

In agreement with Moore, Martin Du Pan, and Buxton,[10] we found an increase in serum α- and β-globulins and a decrease in albumin in pregnancy. We also noted an increase in γ-globulin. Our protein results agree quite well with theirs obtained by electrophoretic means. Since the polysaccharide content of the albumin fraction was increased during pregnancy, there must be an increase in polysaccharide-rich proteins in the albumin fraction. This increase is apparently not due to an increase in the proteose described by Winzler and Burk[11] as polysaccharide determinations on this fraction yielded essentially the same results for both normal and pregnant subjects (averaging 10 mg. per cent for fifteen normal and 8 mg. per cent for six pregnant subjects).

The elevation of the polysaccharide following parturition may be ascribed either to the injury which occurs during delivery or to the tissue repair following this injury. Similar results have been obtained following surgical operations.[7]

Summary and Conclusions

A study was made of the serum nonglucosamine polysaccharide, glucosamine, and protein levels in pregnancy, parturition, and the postpartum state. In late pregnancy the nonglucosamine polysaccharide, glucosamine, and albumin polysaccharide were all significantly elevated. The α- β-, and γ-globulin polysaccharide levels expressed as milligrams per cent were also somewhat elevated, due merely to the increase of these protein fractions in pregnancy. The total serum protein and albumin were significantly depressed, while the globulin fractions were increased in late pregnancy. No difference was found between primigravidas and multigravidas.

Serial determinations made on the same subjects during the course of pregnancy indicated that the serum polysaccharide was noticeably elevated by the sixth or seventh month, and that little change occurred after the eighth or ninth month. Following parturition, the serum polysaccharide rose further, reaching a maximum about the fifth to eighth day, after which it slowly decreased to reach normal levels in thirty to sixty days.

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CONTINUOUS CAUDAL VERSUS SADDLE-BLOCK ANESTHESIA IN OBSTETRICS*

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INDIVIDUALIZATION is of paramount importance in the selection of an agent for the production of obstetric analgesia and anesthesia; and the obstetrician, if he is to select the best method for each patient, must be thoroughly familiar with several methods including both general and regional anesthesia. The introduction of continuous caudal anesthesia by Hingson and Edwards[1, 2, 3] in 1942 and saddle-block or low spinal anesthesia by Adriani, Roman-Vega, and Parmley[4, 5] in 1946 elicited widespread interest. This study was made to compare the relative values of caudal and saddle-block anesthesia and to discuss their advantages and disadvantages. Montgomery and associates[6] made a comparative study of caudal and spinal anesthesia in 1944 and concluded it was an open question whether advantages offered by regional anesthesia compensated for certain intrinsic dangers. Recent refinements in the technique have made the administration of continuous caudal and saddle-block advantageous in many obstetric patients, and we feel that a further comparison is justified.

We do not advocate the routine use of these procedures, but we agree with Andros, Dieckmann,[7] and Masters[8] that any physician with a reasonable amount of training, proper obstetric judgment, and technique can administer both caudal and saddle-block anesthesia for the relief of pain during labor and delivery with a high degree of safety.

The material presented in this report represents 2,043 patients who received continuous caudal or saddle-block anesthesia. These patients were attended by the writers and the resident obstetricians at the Nashville General Hospital and St. Thomas Hospital in Nashville, Tenn.

The patients were divided into two main groups:

Group One.—All patients in this group received continuous caudal anesthesia. There were 1,011 patients, 500 of whom were primiparas and 511 were multiparas.

Group Two.—All patients in this group received saddle-block anesthesia. There were 1,032 patients, of whom 402 were primiparas and 630 were multiparas.

In the management of both procedures it is imperative to have a complete evaluation of the patient before the anesthesia is started. The principal contraindications are those outlined by Hingson, Edwards, and Adriani. Either procedure should be withheld in the presence of such obstetrical complications as placenta previa or abruptio placentae unless pregnancy is to be terminated immediately by cesarean section. Either procedure is ideal in the presence of respiratory infection, tuberculosis, asthma, cardiac disease, with or without decompensation, toxemia, pre-eclampsia, eclampsia, hypertension, diabetes mellitus, and premature deliveries.

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Group One. Caudal Anesthesia

Premedication.—Delvinal Sodium, 6 grains, with Demerol, 100 mg., and/or scopolamine, 1/150 grain, is given when the patient is in active labor with uterine contractions recurring every four or five minutes. Satisfactory analgesia is provided by these drugs in the early first stage of labor until the patient is ready for caudal anesthesia. It not only allays any fear of the needle but assures the patient's full cooperation. Demerol, 100 mg., or scopolamine, 1/200 grain, may be repeated if the patient becomes apprehensive, but usually the head is well engaged by this time and the cervix is 2½ to 3 fingers dilated. However, if the labor is progressing rapidly, caudal anesthesia is administered as soon after the premedication as practicable.

The technique used in this study is that of Hingson and Edwards, first described in 1942, using the 19-gauge malleable steel needle. We would like to emphasize that careful aspiration should be performed several times, and if clear fluid is obtained the procedure is discontinued. As originally advocated, 1.5 per cent Metycaine in Ringer's solution was the only agent used. The smallest amount given in this series was 30 c.c. and the largest amount was 610 c.c. The average amount of Metycaine given was 70 to 150 c.c. The amount of Metycaine and the number of injections depend on the length of labor and the time of starting the anesthesia. If however, the analgesia is permitted to fall, it takes additional time and increased dosage to re-establish the level. We have continued the supplementary injections for a maximum of fourteen and one-half hours with an average of five hours. The shortest time was twenty minutes.

The responsibility of the anesthetist obstetrician does not end with the insertion of the needle. Careful attention to the patient is an equally important prerequisite to success and complete safety, and the patient must be followed closely by a competent attendant throughout labor and delivery. Blood pressure readings were taken before administering caudal and at fifteen-minute intervals after each injection and again after the patient was placed on her back for delivery. If blood pressure fell below 90 mm. of mercury, ephedrine, 1 c.c., was administered intramuscularly or 3 minims intravenously. This occurred in 6.3 per cent in this series.

The patient was allowed to change her position any time she desired, which was usually after two or three hours in the same position. We permit some patients to lie on their backs but the majority prefer to lie on their sides.

It is most important to ascertain the station of the presenting part before removal of the needle or the anesthesia may wear off too soon and some other type of anesthesia will be needed to complete delivery. We have found that it is safe to leave a primipara in her room until the presenting part is seen, and the multipara until the cervix is completely dilated and the presenting part is at the spines. Additional Metycaine is then administered if necessary until the level of anesthesia is at the umbilicus. This is determined by "skin pricking." In following this procedure the anesthesia will be effective for one to two hours and there will be no hurry to deliver the patient.

After the needle is removed the area is sprayed with one of the antiseptic tinctures and the patient prepared for delivery. If the presenting part is on the perineum, delivery usually can be accomplished with outlet forceps in the primipara, with or without episiotomy, or spontaneously in the multipara with the aid of the Kristeller maneuver.

The fully conscious patient is able to take nourishment and an adequate amount of fluids during the course of labor. Nausea and vomiting occurred in 7.4 per cent of Group One, usually at the beginning of the second stage of labor but can occur at any time, especially if the patient is moved too often.

Group Two. Saddle-Block Anesthesia

The same contraindications, indications, and method of premedication were observed in this group as in the caudal group.

The technique used in this series of cases is similar to that outlined by Adriani and Parmley in 1946 with the exception that we used 1.5 c.c. of 3 per cent Metycaine in 5 per cent dextrose solution. We had good results with Metycaine in caudal anesthesia, and we desired to use the same drug throughout our series so that there would be no reason for confusion on the part of the various residents administering the agent. Earlier in this study, however, 106 patients did receive 2.5 mg. of Nupercaine.

The blood pressure was taken every five minutes until it was stabilized and at thirty-minute intervals thereafter. If at any time the blood pressure fell below 90 mm. of mercury, ephedrine, 1 c.c., was given intramuscularly or 3 minims intravenously. This occurred in 15.6 per cent of patients. Observations of the maternal pulse rate and fetal heart rate were made between blood pressure readings.

Nausea and vomiting occurred in 21.3 per cent, usually starting ten to fifteen minutes after the initial injection, and sometimes persisted for an hour or more.

TABLE I. ANALYSIS OF CASES IN WHICH CAUDAL AND SADDLE-BLOCK ANESTHESIA WERE USED

	TOTAL CASES	PRIMIPARAS	MULTIPARAS	ANESTHETIC FAILURES	NAUSEA AND VOMITING	BLOOD PRESSURE BELOW 90 MM. Hg	POSTSPINAL HEADACHE
Caudal	1,011	500	511	10.5%	7.4%	6.3%	None
Saddle-block	1,032	402	630	7.8%	21.3%	15.6%	9.1%

Since there is a great variation in the threshold of pain, there is also great variation in the duration of analgesia in different individuals when the same drug is used. Our shortest duration was twenty-three minutes, and our longest was three hours. The average duration of anesthesia was one hour and forty-five minutes. We endeavor to administer the anesthesia late in the first stage of labor when delivery is expected within two hours. More multiparas were selected for saddle-block because a shorter labor is usually the rule and it was anticipated that one injection would be sufficient to complete delivery. Although we do not hesitate to repeat the injections as needed, only twenty-one patients required a second block, and six patients required a third block. Ninety-six per cent of the patients required a single block.

TABLE II. CAUSES OF FAILURES

	CAUDAL	SADDLE-BLOCK
Unable to enter canal	52	24
Perineal anesthesia only	12	29
Needle misplaced	12	0
Unilateral distribution	12	0
Given too late to be effective	0	23
Emotional instability	6	2
Uterine inertia	6	2
Puncture of dura	3	0
Started too early	3	0
Sensitivity to drug	1	0
Precipitation of drug	0	1
Total failures	107	81

Either anesthesia was classified as a complete failure when no relief of pain was obtained or when it was discontinued prior to completion of the delivery for any reason whatsoever.

There is no doubt that operative deliveries were increased but the majority of patients were delivered by a minor operative procedure. Diminished uterine contractions and relaxed birth canal may account for the high incidence of persistent posterior positions since it is possible that strong uterine contractions forcing the vertex down against a resistant pelvic floor is the greatest aid to spontaneous rotation.

TABLE III. METHODS OF DELIVERY

	SPONTANEOUS	LOW FORCEPS	BREECH EXTRACTION	MID-FORCEPS	OCCIPITO-POSTERIOR	PERSISTENT POSTERIOR	MANUAL ROTATION	FORCEPS ROTATION
Caudal	21.9%	72.5%	4.1%	1.3%	23.6%	93.5%	95%	5%
Saddle-block	24.5%	73.5%	1.9%	0.2%	16.7%	86.5%	97%	3%

The average duration of labor in both groups was 10 hours and 30 minutes in the primiparas and 6 hours and 40 minutes in the multiparas. Labor seemed to be accelerated after the administration of either anesthesia. Only 11 patients had labors of more than 24 hours. One patient with primary uterine inertia had a 36-hour labor. The shortest labor was 55 minutes. The second stage of labor is not significantly increased unless the presenting part is allowed to rest on the perineal floor. The average second stage of labor was 30 minutes. In one case it was prolonged to 2 hours and 30 minutes.

The average blood loss in both groups was 125 c.c. in the primiparas and 75 c.c. in the multiparas. A blood loss of more than 500 c.c. was classified as postpartum hemorrhage and occurred in seven cases, four in the caudal group and three in the saddle-block. All responded favorably to oxytocic drugs and immediate blood transfusion.

Two patients had a temporary respiratory paralysis. One patient in the caudal group received 90 c.c. of Metycaine for a short labor of 1 hour and 30 minutes and paralysis occurred after the birth of the placenta. Paralysis occurred during labor in one patient in the saddle-block group. Both responded to ephedrine and oxygen.

There were no maternal deaths in either group.

The 3 per cent increase in asphyxia in the caudal group may have been caused by the longer duration of anesthesia; the average duration was five hours in this group and on hour and forty-five minutes in the saddle-block group. All infants but one were quickly and easily resuscitated. One infant in the caudal group was severely asphyxiated and required thirty minutes for resuscitation. This child has been followed for four years and is perfectly normal.

TABLE IV. EFFECT ON INFANTS

	BORN ALIVE	SPONTANEOUS RESPIRATION	ASPHYXIA		
			SLIGHT	MODERATE	SEVERE
Caudal	897	93.3%	4.4%	2.1%	0.2%
Saddle-block	946	96.4%	2.6%	1.0%	0

Of the 1,871 infants delivered, forty-four were lost, twenty-three in the caudal group and twenty-one in the saddle-block group, a gross fetal mortality rate of 2.5 per cent and 2.2 per cent. The cause of death is given in the following table.

If we are allowed to deduct the nine infants that died before the onset of labor, two nonviable infants, one with prolapsed cord, and two neonatal deaths from diarrhea and pneumonia, our corrected fetal mortality rate is 1.6 per cent in the caudal group and 1.5 per cent in the saddle-block group.

TABLE V. FETAL MORTALITY

CAUDAL		SADDLE-BLOCK	
Stillborn	15	Stillborn	13
5 before onset of labor		4 before onset of labor	
10 during labor		9 during labor	
2 cerebral hemorrhage		7 premature	
2 cord around neck		1 cerebral hemorrhage	
1 prolapsed cord		1 unknown	
1 abruptio placentae			
1 nonviable			
3 unknown			
Neonatal deaths	8	Neonatal deaths	8
2 full-term		3 full-term	
1 atelectasis		1 atelectasis	
1 cerebral hemorrhage		1 diarrhea (8 days)	
6 premature		1 pneumonia (6 days)	
4 viable		5 premature	
1 nonviable		5 atelectasis	

Convalescence was remarkably smooth in both groups. The patient was returned to her room showing no signs of fatigue and was able to take nourishment when desired. Morphine, $\frac{1}{6}$ grain, and, with some, scopolamine, $\frac{1}{150}$ grain, was given to allay any anxiety that might arise after the anesthesia had worn off. This was repeated as indicated in the first twenty-four hours. Blood pressure was taken at thirty-minute intervals until stabilized. We had no extreme drop in blood pressure in the postpartum period. Backache at the site of the injection occurred in fifty-three cases. All were of a minor type and none required treatment. In the caudal group, headaches were conspicuous by their absence. In the saddle-block group, postspinal headaches occurred in 9.1 per cent and were the only postanalgesic neurological sequelae in either group. All were relieved by aspirin or codeine and sandbags placed to the abdomen. Infection was limited to four cases of superficial cellulitis at the site of the injection, three in the caudal group and one in the saddle-block. All responded to incision and drainage. Only one patient was sensitive to the drug used. No needle was broken in either series.

The incidence of catheterization was not materially increased by the anesthetic agents.

Complications existed in 126 patients. The most common, upper respiratory infection, was present in sixty cases. One patient in the caudal group developed lobar pneumonia but responded readily to penicillin. Forty-two patients had pre-eclampsia and sixteen had hypertensive toxemia. Heart disease was present in five patients and diabetes mellitus in three patients.

Morbidity rates were about the same in both groups as in those who had other types of analgesia and anesthesia.

Summary and Conclusions

Many authors are divided in their preference for continuous caudal or saddle-block anesthesia, although excellent results are obtained from either method. This division arises largely from the advantages and disadvantages peculiar to each method:

CONTINUOUS CAUDAL	SADDLE-BLOCK
Contraindications more numerous	Contraindications less numerous
Can be given earlier and continued longer with complete anesthesia	Used late in labor
More difficult to administer	Easily, rapidly, and more certainly given, readily interchangeable with caudal
Large amount of agent needed	Small amount of agent needed
Blood pressure drop less frequent	Blood pressure drop more frequent
Nausea and vomiting less frequent	Nausea and vomiting more frequent
More trauma to soft parts	Less trauma to soft parts
Infection may be more common	Infection may be less common
Neurological sequelae less	Postspinal headache more common

Our results with both continuous caudal and saddle-block anesthesia were highly satisfactory. We are convinced that both procedures can be administered safely by trained, competent personnel who are familiar with the technique, and are thoroughly aware of the dangers encountered.

In this series we failed to obtain complete anesthesia in 10.5 per cent of the caudal group and 7.8 per cent of the saddle-block group. As our experience increased, our failures decreased.

Premedication as used in this series provides satisfactory analgesia in the first stage of labor and assures a calm, cooperative patient for either continuous caudal or saddle-block anesthesia.

Since continuous caudal anesthesia can be given earlier and continued longer with complete anesthesia, we prefer it for patients with cardiac disease, tuberculosis, and other complications in which it is desirable to avoid the strain and fatigue of labor. On our service, we have almost eliminated cesarean section for these indications. Hypotension, nausea and vomiting, and postspinal headache were not encountered as frequently as in saddle-block anesthesia.

On the other hand, when labor is progressing rapidly, and delivery is expected within one or two hours, saddle-block is more certainly and rapidly administered.

Labor seemed to be accelerated after the administration of either anesthesia. The increased incidence of persistent posterior position and operative deliveries in both groups was not considered a deterrent, since no difficulty was encountered in rotating the occiput, and the majority of operative procedures were outlet forceps deliveries. Blood loss was lessened and the convalescence smoother in both groups.

There is little choice between continuous caudal and saddle-block anesthesia in the effect on the infants, and both are particularly desirable in premature deliveries. Fetal mortality was essentially the same in both groups, 1.6 per cent in the caudal group and 1.5 per cent in the saddle-block group.

The incidence of maternal morbidity was not increased, and there was no maternal mortality in the entire series.

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EFFECT OF DICUMAROL ON THE NURSING INFANT

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TWO important factors have contributed to the hesitancy to use anticoagulants during the immediate postpartum period as prophylaxis or therapy for thromboembolism. The danger of hemorrhagic complications induced by the transmission of the anticoagulant effect across the breast barrier to the infant requires serious consideration when the oral anticoagulant Dicumarol is administered to the nursing mother. Neonatal hemorrhage is still a major problem in obstetrics. Also, the danger of increased puerperal bleeding needs to be kept in mind. If these two hazards could be obviated, Dicumarol could be used safely for the treatment of puerperal thromboembolism and for its prevention.

The need for a prophylactic program in obstetrics is readily appreciated when one inspects the various reports in the literature on the incidence of puerperal thromboembolic complications. For example, the Maternal Welfare Committee of Kings County, New York, reported 794 deaths in 395,655 deliveries from 1938 to 1945.[1] Eighty-nine of these deaths, or 8.9 per cent, were embolic. Eleven died every year from pulmonary embolism. Therefore, if a program could be adapted whereby the majority of vascular disorders could be prevented, then a definite decrease in maternal mortality would be attained. Clinical evidence is steadily accumulating that Dicumarol, when intelligently used prophylactically in postoperative cases[2-5] (United States and the Scandinavian countries) and coronary thrombosis,[6-9] has resulted in a marked decrease in the incidence of thromboembolic complications and embolic deaths. In this report, data will be presented showing the use of this anticoagulant drug in therapeutic doses during the puerperium and its effect on the mother and nursing infant.

Clinical Material and Methods

A series of 125 postpartum cases was used in this study. Each mother received therapeutic doses of Dicumarol and also nursed her infant during her hospital stay. The cases were consecutive and included cesarean sections as well. Two samples of blood for prothrombin studies were obtained at the time of delivery: venipuncture from the mother and puncture of the umbilical vein of the newborn. These determinations serve as a base line in each case. Dicumarol administration was started twelve to twenty-four hours following delivery. Daily prothrombin times were then taken on the mother and baby. In order to insure similarity and comparability of blood samples between the mother and the baby, venipunctures on the infants were done by the femoral-tap method in every infant. The infants were examined daily for any hemorrhagic manifestations and checked monthly at the Well Baby Clinic following their discharge from the hospital. The amount of Dicumarol administered to the mother depended upon the daily prothrombin values. In general, sufficient doses were administered to bring the prothrombin clotting time up to 25 to 30 seconds (40 to 50 per cent of

normal). The initial dose was usually 200 mg. and throughout her stay the average nursing mother received 600 mg. of Dicumarol.

The single-stage method for prothrombin clotting time determination was used throughout this study. Recent investigations reveal that the blood coagulation process, normal and pathological, appears as an interplay of a number of opposing factors.[10] The various components necessary to retard or accelerate clotting are present in the circulating blood. Hence, the fluid state is maintained as a result of a dynamic balance between factors accelerating coagulation and those inhibiting the process. Some evidence has been reported that during the postpartum period there is a shift in favor of potential thrombogenesis.[11] Shortened clotting times of diluted plasma as determined by the one-stage prothrombin clotting time method[11] and increased resistance to Dicumarol have been observed in lactating animals.[12] The modified Quick's one-stage procedure measures the resultant effect of the opposing groups of clotting components rather than the amount of any single entity.[11, 13, 14] Dicumarol has been administered in conservative dosage sufficient to offset the increase in the thrombogenic property of the coagulation accelerating factors in circulating blood.

The thromboplastic reagent for this test was prepared by acetone extraction of fresh rabbit brains with some modifications[14] after the method described by Quick.[15] No preparation was used unless it yielded 14 to 15 seconds for normal undiluted plasma and 75 to 85 seconds for a 12.5 per cent saline solution. The modifications proved effective in maintaining reproducible values in the tests. Uniformity is most essential when comparability of data is required. In this study the clotting power of the nursing baby is compared to that obtained from the mother receiving Dicumarol. Routine tests consisted of determinations on undiluted and saline-diluted (12.5 per cent) plasma. The mother and baby plasmas were run simultaneously. The relative degree of inhibition of the clotting mechanism, in terms of percentage of normal after administration of Dicumarol, was obtained from an accumulated series of saline dilution curves of normal plasmas.

Even though Dicumarol has proved to be reasonably free from hemorrhagic complications in the present series of cases, each patient was carefully watched and when the prothrombin clotting time was found to be above 35 seconds (30 per cent normal), 72.5 mg. of a synthetic vitamin K derivative, Hykinone, were given intravenously. Such a procedure increased the margin of safety and prevented hyperreaction to the drug. A synthetic vitamin K derivative (4.8 mg.) was administered intramuscularly every eight hours to the mother while in labor.

The majority of postpartum patients show definite resistance to Dicumarol and necessitate large doses of Dicumarol before the prothrombin time is affected. However, when the prothrombin time does begin to change it increases rapidly and must be checked daily. A few patients were found to be hyperreactors to Dicumarol. For these reasons the maintenance and production of a selected level of decreased prothrombin activity by Dicumarol becomes an individual problem in each case.

Results

In this series of cases higher prothrombin clotting times were maintained than in our routine prophylactic program in order to demonstrate that there is no effect on the infant and no increased puerperal bleeding. Many of the patients were carried as low as 30 per cent of normal (35 to 45 seconds for undiluted plasma). A prothrombin activity of 40 to 50 per cent normal (25 to 30 seconds by the method used in this study) is recommended as sufficient prophylaxis against thromboembolism in this clinical category, and greatly diminishes the potential hemorrhagic hazard.

An analysis of the accumulated data reveals that as the mother's prothrombin clotting time became elevated as the result of Dicumarol administration, the value remained unchanged for the infant. There was not a single instance wherein the infant's prothrombin clotting time was prolonged by the mother's ingestion of Dicumarol.

Table I comprises a representative portion of the 125 cases, comparing the mothers' and infants' prothrombin clotting times before receiving any Dicumarol, and then six days after the nursing mother had been receiving therapeutic doses of the anticoagulant. In each case it will be noted that the infant's prothrombin time is normal on the sixth postpartum day, whereas the mother's is markedly increased on the same day.

TABLE I. PROTHROMBIN CLOTTING TIME: SECONDS

BEFORE DICUMAROL ADMINISTRATION TO MOTHER				AFTER DICUMAROL ADMINISTRATION TO MOTHER			
MOTHER		BABY		MOTHER		BABY	
UNDIL. PLASMA	12.5 PER CENT PLASMA	UNDIL. PLASMA	12.5 PER CENT PLASMA	UNDIL. PLASMA	12.5 PER CENT PLASMA	UNDIL. PLASMA	12.5 PER CENT PLASMA
16	63	15	92	39	400	14	89
15	47	14	86	15	132	14	71
14	54	16	120	30	400	14	74
16	61	16	151	28	200	15	96
14	43	16	228	32	400	14	71
15	54	15	122	16	176	15	81
15	50	19	236	44	400	14	89
14	57	14	93	27	178	15	87
14	48	14	79	45	400	14	74
13	50	15	94	26	200	14	100
13	58	13	100	25	157	14	90
15	50	19	122	35	400	14	69
14	58	17	121	29	227	14	85
13	41	14	96	33	400	15	79
15	84	19	174	27	163	13	89
14	66	15	98	30	400	15	84
13	53	15	103	23	156	14	92
13	42	16	98	31	400	14	92
14	50	14	87	33	400	14	90
14	52	13	74	38	400	13	82
14	57	20	153	24	144	14	86
13	61	15	84	32	400	13	86
13	52	15	92	28	236	14	100
14	50	17	98	33	400	13	71
12	48	15	85	32	400	14	92
13	46	14	87	29	263	14	89
16	56	13	64	32	200	12	61
15	84	19	174	27	163	13	89
14	54	18	120	25	139	14	100
14	35	23	107	26	145	14	84
12	51	15	82	29	255	14	91
14	50	20	192	22	136	13	56
13	54	14	115	24	136	14	95
14	60	16	123	24	136	14	84
15	58	14	91	24	171	15	107

Inspection of the data presented (Table I) reveals that before Dicumarol administration the prothrombin clotting time of diluted (12.5 per cent) maternal plasma is consistently shorter than that of the newborn. The values range from 35 to 84 seconds (median, 55 seconds) for maternal blood compared to 64 to 236 seconds (median, 115 seconds) for cord blood. The majority of the values for undiluted plasma, both mother and baby, were not separated by more than two or three seconds. There are a few exceptions where definite elevation of the

prothrombin time of the newborn was found. The mothers' prothrombin time (undiluted plasma) ranged from 12 to 16 seconds (median, 14 seconds). These data are in confirmation of an earlier study.[11]

After administration of Dicumarol to the mother, regardless of the degree of inhibition of the maternal blood-clotting system, the prothrombin clotting time of the nursing infants ranged from 13 to 15 seconds for undiluted plasma. By contrast, the prothrombin clotting time of undiluted maternal plasma ranged in some instances from 35 to 45 seconds. Here we have a demonstration of the lack of anticoagulant effect on the nursing infant from the Dicumarol passing the breast barrier.

Table II illustrates the gradual return to normal from the physiological decrease in prothrombin activity at the time of birth of the infants in six cases. Of course, each child did not show such a progressive return to normal because of the known wide physiological variations in the first week of life, but by the sixth day of life the prothrombin time was normal in each of the 125 cases regardless of the fact that the mother was receiving Dicumarol.

TABLE II. PLASMA PROTHROMBIN CLOTTING TIME

DAYS POST PARTUM	CASE 1 PLASMA		CASE 2 PLASMA		CASE 3 PLASMA		CASE 4 PLASMA		CASE 5 PLASMA		CASE 6 PLASMA	
	UNDIL.	12.5%	UNDIL.	12.5%	UNDIL.	12.5%	UNDIL.	12.5%	UNDIL.	12.5%	UNDIL.	12.5%
1	17	106	32	400	16	228	19	174	16	104	17	121
3	14	73	26	274	14	100	16	91	15	119	14	116
5	15	64	16	84	14	71	13	89	14	80	14	85

The data presented in Tables I and II also reveal the ineffectiveness of vitamin K administration to the mother before delivery as prophylaxis for hypocoagulability of the blood of the newborn.

These infants were followed clinically for any evidence of Dicumarol toxicity while in the hospital and for the first six weeks of life. In not a single instance was there any effect during this period, and at the end of the sixth week each infant was normal. The pediatricians were consulted frequently as to whether they had observed any effect on the infant, but none had. Since the completion of this series, 1,500 other nursing infants of mothers given Dicumarol have been followed clinically, without taking daily prothrombin times on the infants, and no hemorrhagic manifestation has been observed at any time.

In this series of cases there were no cases of serious postpartum hemorrhage. One patient developed a slow, persistent oozing of blood from the episiotomy on the fifth day. The bleeding was from the mucous membrane and a mattress suture was all that was necessary to stop the bleeding. This case is considered as a minor complication of Dicumarol.

Although the number of patients in this series is small, there was not a single instance of thromboembolism or neonatal hemorrhage. Similar results have been obtained in a larger series now under investigation.

Side reactions, such as nausea, vomiting, diarrhea, have been minimal.

Comment

Anticoagulant drugs that are to be used routinely as a prophylaxis against puerperal thromboembolic disease should have a wide margin of safety. Counteractants should be available to check and to restore to normal the depressed blood-clotting mechanism if bleeding occurs, or if the degree of inhibition of the blood-clotting components progresses beyond the desired range and hemorrhage is anticipated, or if a serious hyperreactor to the drug is encountered. Synthetic

vitamin K derivatives,[16, 17] vitamin K_1 oxide,[18] whole blood and blood plasma[19, 20] have been used with varying degres of success depending upon the severity of reaction. It would also be desirable to determine whether Dicumarol is secreted by the breast of the mother in amounts sufficient to affect the clotting mechanism of the nursing infant. Secretion of the drug, however, can be ascertained only by its effect on the prothrombin clotting time of the nursing infant. Thus, the data presented in this paper indicate, not that Dicumarol is not secreted by the breast and ingested by the nursing infant, but that the anticoagulant effect of Dicumarol on the blood-clotting system of the infant is negligible, notwithstanding the reported sensitivity of the newborn.[21]

It is not the purpose of this paper to present a critique of laboratory methods, even though it is the most important issue involved, but rather to present clinical data obtained as the result of an elected routine program. Much work still remains for the satisfactory development of adequate procedures. There are undoubtedly more precise one-stage methods than the one used in this paper. The two-stage procedure, as simplified by Seegers[10] and his co-workers, yields data of a quantitative nature for some of the clotting components.

The precise degree of inhibition of the blood-clotting system for effective prophylaxis against thromboembolism is another point which has not been established with certainty. The conservative pattern of depressing the clotting mechanism to just below 50 per cent of normal has proved effective in several clinical categories investigated at Mercy Hospital: surgery (gangrene[24] and postoperative[5]), medicine (coronary thrombosis[7]), and obstetrics (postpartum thromboembolism[25]). Only further accumulation of clinical data will establish the selected effective and safe level of decreased clotting activity of blood. It must be borne in mind that the degree to which anticoagulation is to be pushed may depend on the type of case. Thus, previous history of thromboembolic disease may warrant drastic anticoagulation as opposed to conservative depression of the clotting components. In routine prophylaxis, on the other hand, conservative inhibition may be effective, as has been our experience.

The rationale for administering Dicumarol to postpartum patients was to counteract the potential hypercoagulability of maternal blood, as demonstrated by laboratory test[11] and by resistance to this anticoagulant drug.[12] It is to be admitted that such a procedure controls only one of several factors in the etiology of thromboembolic disease. The clinical results obtained, however, have been most encouraging.[4-9, 24]

Earlier studies[11] revealed that maternal blood manifested evidence of hypercoagulability compared with normal when diluted plasma was used, while the newborn revealed hypocoagulability or prolonged prothrombin times. These findings in the mother were considered as a detection of increased prothrombin activators and were interpreted as indicating a predisposition to puerperal thromboembolism. An hypothesis was then proposed, on the basis of a balance between prothrombin activators and inhibitors, that an excess of activators was present in maternal blood during parturition, with a deficiency in the blood of the newborn, rather than a decrease of a major clotting component such as prothrombin. A one-stage procedure[14] for prothrombin activity was used in both studies. The above postulate is supported by the work of Randall and Randall,[26] who interpreted the decrease in prothrombin activity of the newborn to be due to a deficiency of an accelerator factor for the conversion of prothrombin to thrombin. Similarly, Owren[27] (in an adult) showed that prothrombin clotting times, as determined by the one-stage procedure, may be due to a decrease of a factor other than prothrombin.

Dicumarol has been used conservatively by us, with the idea of counteracting the effect of the excess of activators or accelerators present in maternal blood, and so inhibiting thromboembolic disease. The same rationale has been used

during the investigation of other clinical conditions, surgical[5] and medical.[7] Evidence is accumulating[22, 23] that Dicumarol affects the activator components of the blood-clotting system to a certain degree and also inhibits prothrombin production by the liver. In anticoagulation the important physiological effect to accomplish is the depression of activators or accelerators of the primary clotting component, prothrombin, rather than the drastic inhibition of prothrombin production. When prothrombin production by the liver is inhibited it is then that hemorrhage difficult to control may be encountered and fatality from this cause may follow. Real prothrombin deficiency in hemorrhagic disease is serious. The conservative depression of the clotting mechanism to just below 50 per cent of normal with Dicumarol permits considerable leeway with regard to the incidence of bleeding hazards.

Experimental studies[28] have shown that when relatively large doses of Dicumarol are given to lactating animals, the nursing pups may bleed and die. It is recognized that the nursing animal is sensitive[21] to Dicumarol, which may be based upon the physiological decrease of activating factors for prothrombin.[11, 27] However, the doses of Dicumarol given to mother rats were relatively much greater than the doses which are given clinically. In fact, they were sufficient to produce generalized bleeding and death in the mother rats as well. This situation cannot be compared to the controlled administration of therapeutic doses of Dicumarol to the human subject. Here again, notwithstanding a weakened clotting system of the newborn, conservative administration of Dicumarol has resulted in the anticoagulant being secreted by the breast and ingested by the infant in insufficient amounts to affect the clotting system of the infant. Moreover, the impression of prevention of postpartum thromboembolism with this anticoagulant is becoming apparent in our rapidly accumulating series.[25] Thus it eventuates that the use of Dicumarol in this way is doubly justified, which is in contrast to the general assumption, based on Field's[28] and Quick's[21] work, that the administration of Dicumarol to the nursing mother is contraindicated.

Barker and co-workers[4] reported a series of nineteen postpartum cases complicated with thromboembolic disease and treated with Dicumarol. Two of these mothers nursed their infants and repeated prothrombin times showed values which were normal, even though the prothrombin activity of the mothers was between 10 to 20 per cent normal.

Our data showing that controlled Dicumarol therapy does not increase puerperal bleeding is confirmed by other reports. Davis and Porter[29] used Dicumarol in the treatment of postpartum thrombosis in forty-three cases without a single instance of spontaneous bleeding in spite of large doses. Barnes and Ervin[30] were unable to find that this drug significantly increased puerperal blood loss.

Conclusions

1. Dicumarol can be administered to nursing mothers without hemorrhagic hazards to the infant.

2. Therapeutic doses of Dicumarol were administered to 125 nursing mothers without affecting the prothrombin activity of the nursing infant.

3. Clinically, there was no evidence of hemorrhagic manifestations in any infant.

4. Only one case of minor postpartum bleeding was encountered and no instances of thromboembolism.

5. Carefully standardized prothrombin clotting time methods are essential for the control of the Dicumarol effect.

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SODIUM PREGNANDIOL GLUCURONIDATE DETERMINATIONS IN THREATENED ABORTION*

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IT IS now generally accepted that progesterone, in the human being, is metabolized to pregnandiol, which is then conjugated with glucuronic acid and excreted in the urine as sodium pregnandiol glucuronide (NaPG). Hence NaPG is present in the urine in the postovular phase of the menstrual cycle due to the production of progesterone by the corpus luteum spurium, and in pregnancy due to the production of progesterone by the corpus luteum of pregnancy and the placenta.

Numerous investigators[1-6] have demonstrated that the curve of excretion of NaPG in pregnancy is fairly uniform although individual variations are frequent. Usually the excretion of NaPG for the first ten to twelve weeks of gestation equals or slightly exceeds that for the postovular phase of the menstrual cycle (6 to 10 mg. pregnandiol per twenty-four hours). At this time (tenth to twelfth week) the excretion begins to rise so that at its peak at about the thirty-eighth week 60 to 100 mg. of pregnandiol are excreted per twenty-four hours.

The increased NaPG excretion at the tenth to twelfth week is due to the onset of elaboration of progesterone by the placenta which begins at this time.[1] Simultaneously there is a retrogression of the corpus luteum. Usually this transfer of the site of progesterone production from the corpus luteum to the placenta is smooth and overlapping so that at no time does there exist a deficiency of the hormone. Where the corpus luteum fails before the placenta takes over its function, a period of progesterone deficiency results which is thought to be the cause of many of the frequent instances of threatened abortions and abortions at this period of gestation.[9]

Considerable work has been done showing the correlation of failure of continuation of NaPG excretion with signs of threatened abortion, and the progress of threatened abortion to completion where the failure of NaPG excretion (and progesterone production) continues.[1, 2, 4, 7-12] Most of the investigators stress the fact that in cases of threatened abortion the levels of pregnandiol are of considerable prognostic value. Where the levels are high, the pregnancy continues; where the levels are low or absent, the pregnancy terminates. Usually the methods of Venning or of Astwood and Jones were employed in the determination of pregnandiol excretion. In 1946, Guterman,[13] employing his method for the determination of urinary pregnandiol, investigated a series of seventy-three cases of threatened abortion. He found that, where persistent negative values or positive values becoming negative obtained, 97 per cent of patients aborted, whereas, where positive values or negative values becoming positive obtained, only 12 per cent aborted. Since his method

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is markedly simplified and results can be obtained easily the same day, the determination of urinary pregnandiol assumes a practical value in the management of cases of threatened abortion. Bender[14] (1947), using Guterman's method in a series of twenty-eight patients with threatened abortion not receiving hormonal therapy, found that in instances where positive (more than 6.0 mg. per 24 hours) results obtained 23 per cent aborted, whereas where negative results obtained 83 per cent aborted.

The present paper is a summary of the authors' experiences with pregnandiol determinations in a series of 115 consecutive cases of uterine bleeding in early pregnancy.

Method

Two methods for the assay of urinary pregnandiol were employed in this study. One is the original Guterman procedure.[15] The second is a modification previously described by the authors.[16] In some instances only the original or the modified technique is employed; in others, both. At all times the determinations were done quantitatively on twelve- or twenty-four hour summaries.

Results

Results are calculated as to milligrams of pregnandiol excreted per twelve hours. Using the Guterman technique values below, 3.0 mg. per 12 hours are considered negative, 3.0 to 3.99, doubtful; 4.0 and above, positive. Using the modified technique, values below 1.0 mg. are considered negative; 1.0 to 1.24, doubtful; 1.25 and above, positive. Five groupings are made: I. persistent positive; II. persistent negative; III. positive falling or becoming negative; IV. negative becoming positive; V. doubtful or irregular. The findings in each category are listed in Tables I to V.

Comment

A. *Persistent Positives.*—In 29, or 64 per cent, of the "persistent" positive cases, the pregnancy continued. Of those that failed to continue, there were: (1) two instances of placenta previa; (2) one instance of fibroid uterus; (3) two instances of tubal pregnancy; and (4) eight instances in which only a single pregnandiol determination was carried out.

Pregnandiol present in the urine of any particular collection period probably represents the progesterone available to the organism twenty-four to forty-eight hours previously. Hence, the finding of a single positive pregnandiol value associated with bleeding in pregnancy does not indicate that the bleeding or subsequent abortion may not be on the basis of progesterone deficiency. This is especially true since the single determination may have been carried out during a period of rapidly falling progesterone production. Subsequent determinations in these instances would yield progressively lower or negative values.

TABLE I. PERSISTENT POSITIVE

	NO. OF CASES	PER CENT
Carried	29	64
Aborted	16	36
Total	45	100

TABLE I. (CORRECTED)

	NO. OF CASES	PER CENT
Carried	29	91
Aborted	3	9
Total	32	100

Of the 16 cases in which the pregnancy failed to continue, therefore, there were 5 instances of mechanical factors, 8 instances of single determinations, and only 3 instances in which no explanation is offered. The corrected data indicate that 91 per cent of the persistent positive cases continued. See Table I corrected.

B. *Negative Becoming Positive.*—In the 4 cases of negative becoming positive, only one patient failed to carry. This was a case of hydatid mole.

TABLE II. NEGATIVE BECOMING POSITIVE

	NO. OF CASES	PER CENT
Carried	3	67
Aborted	1	33
Total	4	100

C. *Persistent Negative.*—In the 35 cases of "persistent" negative values, only two patients carried. In these two cases only single determinations were carried out. All workers in the field have shown that in apparently normal pregnancies occasional periods in which no pregnandiol is excreted occurs. The data are not corrected for these instances of single negative determinations.

TABLE III. PERSISTENT NEGATIVE

	NO. OF CASES	PER CENT
Carried	2	6
Aborted	33	94
Total	35	100

D. *Positive Becoming Negative or Falling.*—Of the 24 cases only one patient carried. In this instance, two determinations five days apart were carried out and no explanation is offered.

TABLE IV. POSITIVE BECOMING NEGATIVE OR FALLING

	NO. OF CASES	PER CENT
Carried	1	4
Aborted	23	96
Total	24	100

E. *Doubtful and Irregular.*—Doubtful and irregular determinations existed in 7 cases. Six of these patients aborted, only one carried. In the case of the one patient who carried, only a single determination was done. A correction is made for this single doubtful determination. See Table V corrected.

TABLE V. DOUBTFULS AND IRREGULARS

	NO. OF CASES	PER CENT
Carried	1	14
Aborted	6	86
Total	7	100

TABLE V. (CORRECTED)

	NO. OF CASES	PER CENT
Carried	0	0
Aborted	6	100
Total	6	100

Summary and Conclusion

In cases of threatened abortion, characterized by uterine bleeding and not associated with known mechanical factors, in which the pregnandiol values are persistently positive or become positive after a temporary drop the pregnancy would be expected to continue. This was found true in thirty-two, or 89 per cent, of thirty-six cases (Table VI).

TABLE VI. PREGNANDIOL VALUES INDICATING CONTINUATION OF PREGNANCY

	NO. OF CASES	CARRIED	ABORTED
Persistent positive	32	29	3
Negative becoming positive	4	3	1
Total	36	32 (89%)	4 (11%)

In the cases in which negative, falling, or irregular pregnandiol values are obtained, abortion would be expected. This was found true in sixty-two, or 95 per cent, of sixty-five cases (Table VII).

TABLE VII. PREGNANDIOL VALUES INDICATING ABORTION

	NO. OF CASES	CARRIED	ABORTED
Persistent negative	35	2	33
Positive falling	24	1	23
Doubtful irregular	6	0	6
Total	65	3 (5%)	62 (95%)

An over-all correct prognosis of 93 per cent is obtained (Table VIII).

TABLE VIII. CORRELATION OF PROGNOSIS AND CLINICAL RESULTS

PROGNOSIS	NO. OF CASES	CORRECT	FALSE
To carry	36	32	4
To abort	65	62	3
Total	101	94 (93%)	7 (7%)

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IN VIVO COLORING OF PELVIC LYMPH NODES WITH INDIA INK

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WITH the renewed interest in the radical surgical treatment of carcinoma of the cervix, stimulated by the work of Meigs, Brunschwig and others, there are being done throughout the United States a steadily increasing number of radical panhysterectomies with and without pelvic lymphadenectomy. Unfortunately, many of these tedious and prolonged operations are being undertaken by inadequately trained surgeons with consequently unsatisfactory results. This course of action will undoubtedly adversely influence the over-all statistics of what might well be one of our most effective weapons against carcinoma of the cervix. We have been convinced by the demonstrations of Taussig and Meigs that the operation would be incomplete and inadequate unless the pelvic nodes were removed. To aid in the attaining of this ideal, as well as to aid in teaching the operation, it was suggested by one of us (G. W.) that India ink might be used to color the nodes black and thus make their identification easier.

The India ink used* is an aqueous colloidal suspension of carbon black, being neutral or slightly alkaline in reaction, and containing edible gelatin and shellac gum. India ink preparations in general are well known for their suitability as a coloring medium for in vivo studies of the lymphatic system. Since carbon forms a nonionizing colloid, the particles are picked up almost solely by the lymphatics and deposited in the various nodes along the chain.

Technique

The technique of injection found most suitable and simple is as follows: The cervix and vaginal vault are prepared with a dry sponge and painted with an aqueous antiseptic. The anterior lip of the cervix is grasped with a single-toothed tenaculum, and 0.5 c.c. of autoclaved India ink solution, one part of ink to two or three parts of sterile distilled water, is injected into the lateral surface of the cervix at three and nine o'clock, the solution being placed just under the mucosa. A tuberculin syringe, because of its small diameter, and a 24-gauge needle are used for the injection. No narcotic or sedative is necessary in most cases, as there is no more pain associated with the procedure than with any hypodermic injection.

The technique was developed on staff patients who were to have laparotomy for some other reason, and varying amounts of different dilutions of India ink were injected at varying time intervals before surgery. To date, more than forty patients have had cervical injections following the above technique, three of whom had carcinoma of the cervix for which a complete Wertheim-type operation was done. The other patients had myomas, chronic pelvic inflammatory disease, benign ovarian tumor, or a combination of these.

*Manufactured by the Higgins Ink Company of New York.

Results

In all patients on whom the previously described technique was used, the pelvic lymph nodes, including all of the iliac nodes, the obturator nodes, and the lower presacral nodes, were distinctly colored and readily visible after very little dissection of retroperitoneal fat (Fig. 1). In one thin patient the nodes over the sacral promontory could be seen through the peritoneum before dissection was started, but this was unusual. The time from injection of the cervix to laparotomy was usually from sixteen to twenty-four hours, with extremes of four hours and forty-two three-fourths hours. In those patients who were injected from sixteen to twenty-four hours before surgery, the gross coloring of the nodes was unaffected by time of the menstrual cycle, age of patient, presence of severe chronic pelvic inflammatory disease, or carcinoma in the cervix. As early as four hours after injection of the cervix, the obturator and lower iliac and hypogastric nodes may be colored grey, but apparently maximum coloring is obtained after about eight hours, and is still present after over forty hours.

Fig. 1.—Large lymph node dissected out and lying in situ below right common iliac artery.

In none of the patients was there any gross or microscopic evidence of inflammatory reaction at the site of injection in the cervix. In seven patients nodes were sent to the laboratory of pathology for study. In only one patient did the nodes show subacute inflammation, and this was attributed to the chronic inflammatory disease that was present in the pelvis. In no case was the architecture or cellular detail of the node distorted or obscured. The carbon granules in the nodes, which were apparently aggregates of the submicroscopic colloidal particles, were almost all within phagocytic cells which were distributed mainly under the capsule and in the germinal centers, although they could be found almost anywhere in the node. In none of the patients was there discoloration of any tissue other than the nodes and the cervix at the site of injection.

Comment

The method of injection presented above is the best of several techniques tried. A larger volume of ink was used at first, but gave no more intensive coloring of the nodes and had two distinct disadvantages. First, the larger volume was more painful to inject, and second, it diffused through so much tissue near the cervix that visualization for dissection became difficult.

Early in the series the ink was injected into the substance of the cervix with a long 22-gauge needle, but soon a small "hypo" needle was substituted, and the injection made into the loose connective tissue just under the mucosa.

An interesting sidelight appeared in several of the patients in whom the injection was made on only one side of the cervix. In sixteen to twenty-four hours the nodes on the side of injection were colored as usual, and the nodes on the opposite side were also colored, though not so intensely. Since the injected mass remains in a small volume of tissue, definitely limited to one side of the cervix, a profuse lymphatic anastomosis across the midline must be present in the cervix.

Summary

An in vivo method of coloring the lymph nodes draining the region of the uterine cervix is presented, using India ink solution injected preoperatively. In over forty patients it consistently caused the nodes to be colored black, and did not discolor any other tissues. In no case was the architecture or cellular detail of the nodes distorted or obscured. The method is presented as an aid to complete removal of all nodes draining the cervix in the Wertheim-type operation for cervical carcinoma, and particularly as an aid to teaching the operation.

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A MANEUVER FOR THE SIMULTANEOUS DELIVERY OF CHIN-TO-CHIN LOCKED TWINS

ALBERT P. KIMBALL, M.D., AND PHILLIP R. RAND, M.D., SAN DIEGO, CALIF.

(From the Mercy Hospital)

NEARLY every textbook on obstetrics contains some reference to the locking of twins as a cause of multiple pregnancy dystocia. The infrequency of occurrence of locking twins usually quoted as one in 90,000 deliveries makes the accumulation of cases rather difficult.

Chin-to-chin locking of twins makes up such a small proportion of the total locked twins reported, that its incidence must be extremely rare. In our survey of the literature, nearly every case reported has resulted in dystocia necessitating the decapitation of the first twin after its death due to delayed delivery. It, therefore, seems most appropriate to publish both the case report and the procedure used for overcoming this situation, in order that additional maneuvers might be available to the unfortunate obstetrician who in the future may be faced with this problem.

Case Report

Mrs. R. D. S., aged 24 years, gravida iii, para ii, 37 weeks pregnant, was admitted to the hospital at 10:15 P.M. on April 11, 1949. Membranes had ruptured at 9:30 P.M., contractions began at 9:45 P.M.

Her first pregnancy resulted in a normal delivery of a viable female, weight 6 pounds, 10 ounces, after one hour of labor. The second pregnancy resulted in a normal delivery of a viable female weighing 7 pounds, 10 ounces, after 43 minutes of labor. Her usual weight is 99½ pounds. She is short, light of structure, has fine features, and a normal pelvis. This pregnancy was entirely normal. Twins were diagnosed at 27 weeks of pregnancy by palpation and auscultation, and confirmed at 32 weeks by x-ray examination.

Forty-five minutes after the onset of contractions, she was first examined, the cervix being completely dilated, and the first twin presenting a frank breech left sacroanterior. Under gas anesthesia and with forcible contractions, an assisted breech delivery was accomplished with no difficulty including delivery of the arms. It was noticed at this time that the entire breech, trunk, and shoulders tended to ride more anteriorly under the pubis than is usual with the attempt at keeping the aftercoming head flexed. At this time, examination revealed the second twin's head engaged in the right occipitoposterior with the neck of the undelivered breech pushed forward against the symphysis pubis. A brief attempt to disengage the chin-to-chin locking was unsuccessful. No amniotic fluid could be palpated before the second twin's head, and it was supposed that the second bag of waters had ruptured. The Piper forceps were applied to the vertex of the second twin for a test of delivery with light traction. The second twin's head was delivered easily. The second amniotic sac was ruptured artificially, no fluid being noted. By placing the left hand on the shoulders of the incompletely delivered breech, and the right hand on the occiput of

the incompletely delivered vertex, a simultaneous delivery was accomplished by flexion. A fused placenta with two cords uniovular was expressed with no difficulty. There was no postpartum bleeding. A deep median episiotomy which had not extended was repaired.

The first twin, a living female, weighing 4 pounds at birth, was discharged on May 1, 1949, weighing 5 pounds, 11 ounces. The second twin, a living female weighing 4 pounds, 12 ounces at birth, was discharged from the hospital on April 24, 1949, weighing 5 pounds, 11 ounces. The mother was discharged on the fifth postpartum day without her children.

FIG. 1

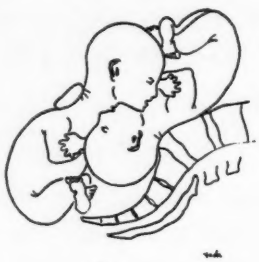

FIG. 2

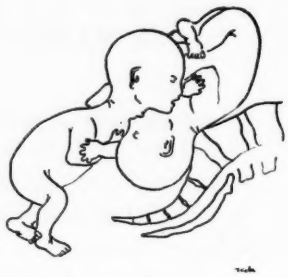

FIG. 3

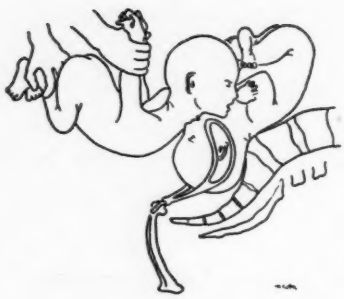

FIG. 4

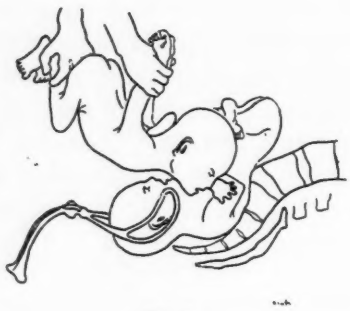

FIG. 5

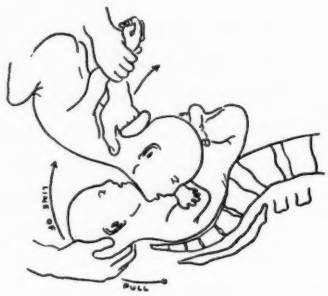

FIG. 6

Fig. 1.—Reveals the position of the breech and vertex twins at the time of first examination.

Fig. 2.—Reveals the breech as it was crowning on the perineum.

Fig. 3.—Reveals the position of the breech and vertex at the time of assisting in the delivery of the arms and shoulders.

Fig. 4.—Reveals the resident's hands holding the extremities of the undelivered breech while the Piper forceps were applied to the vertex of the second twin.

Fig. 5.—Reveals the positions of the two heads at the completion of the delivery of the vertex of the second twin.

Fig. 6.—Reveals the maneuver of simultaneous delivery and the direction of manual traction used.

On June 4, 1949, a six weeks postpartum examination revealed a flabby abdomen, slightly relaxed perineum, perfectly normal cervix. The uterus and adnexa were normal in size, shape, position, mobility, consistency, and support.

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A SUGGESTED MODIFICATION FOR THE OBSTETRICAL FORCEPS TO AVOID TRAUMA

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NOTWITHSTANDING the many improvements since the introduction of the obstetric forceps, the instrument still takes a high toll in traumatic injuries. To lessen these hazards, the "rubberized forceps" is suggested. Any type of forceps can be rubber cushioned. The blades are first cleaned and dried, then dipped in liquid latex.* In about twenty minutes the latex has dried. The blades are then dipped in a coagulant compound and finally dipped again in latex After the first dipping, the latex layer is about 0.001 to 0.003 inch in thickness. After the redipping, about 0.015 inch thickness is added. When finished, the latex covering is about six to eight times the thickness of newspaper.

The rubber-cushioned forceps may be sterilized in the autoclave at 250° C. for fifteen minutes.

With proper application and skillful handling the rubberized forceps is less traumatic than the usual forceps, especially during rotation. The rubberized forceps offers more friction, which tends to prevent slipping of the blades.

Notwithstanding the advantages stated, it must be emphasized that with wrong application the compression trauma from the rubberized forceps is just as great as with the conventional forceps.

1141 PARK AVENUE.

*The latex used in the preparation of the forceps described in this article is called Vultex, a product obtainable from the General Latex and Chemical Corporation, Cambridge, Mass.

AN IMPROVED PEDICLE CLAMP

CHENEY M. STIMSON, M.D., PHILADELPHIA, PA.

THE principle of the clamp here illustrated embodies a blunt, upwardly curved, protruding lower jaw, the smooth, protruding part, a continuation of the lower jaw, extending well beyond the bite of the instrument. Thus, in addition to its use as a clamp, the instrument, by means of the protruding lower jaw, can also be employed as a dissector, as a piercer, and as a guide for the application of the ligature, once the pedicle is clamped and cut.

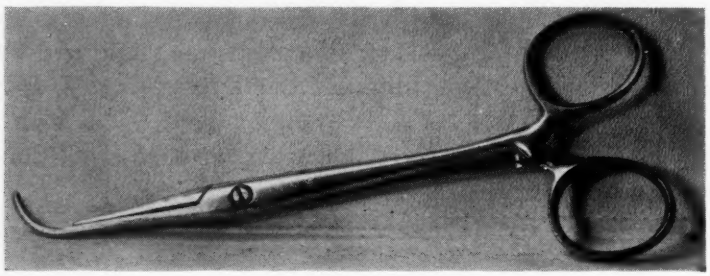

Fig. 1.

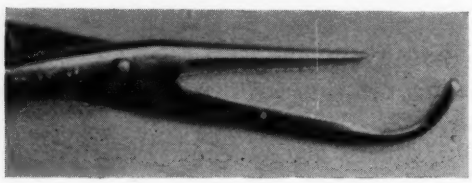

Fig. 2.

The principle may be applied to almost any kind of pedicle clamp, the length, convexity, and bluntness or sharpness of the protruding lower jaw being fashioned in accordance with the size and uses for which the instrument is intended. Hence, a clamp of this design for use on such structures as the cystic duct, the thyroid vessels, varicose veins, etc., would naturally be smaller and lighter—about the size of the ordinary hemostatic forceps—than would one designed for use on the uterine arteries, the kidney pedicle, or other like structures.

The advantage of this clamp is that the curved, protruding lower jaw will at times facilitate the identification, fixation, clamping, and ligation of deeply situated structures.

So far as I have been able to determine, no similar pedicle clamp has heretofore been presented.

167 HARVEY STREET

Department of Reviews and Abstracts

Selected Abstracts

Malignancies

Graham, Ruth M., and McGraw, John: An Investigation of "False Positive" Vaginal Smears, Surg., Gynec. & Obst. **90**: 221, 1950.

The purpose of this paper is to report an investigation of false positive vaginal smears encountered in the Vincent Memorial Hospital Laboratory since 1943. The uteri of eight patients known to have positive vaginal smears which were unconfirmed by clinical or biopsy study were submitted to special investigation. Although none of these uteri showed evidence of gross tumor after operation, four of them were eventually proved to harbor carcinoma in situ of the cervix. Four uteri failed to reveal any lesions which could be diagnosed as carcinoma, although three were completely sectioned serially. Smears from three of these patients were thought to be consistent with adenocarcinoma and the cells in the last smear were not sufficiently well differentiated to suggest the type of epithelium from which they were derived. In addition to the special study of eight uteri, slides of seventy "false positive" smears were reviewed. In sixty-two of these, the positive report had been rendered on the basis of cells previously thought to be carcinoma but now recognized as degenerative histiocytes, abnormal basal cells, or endocervical cells. In the remaining eight cases, the smears still met the criteria for diagnosis of malignancy used in this laboratory. Of these eight smears, five were consistent with fairly well-differentiated adenocarcinoma. It would appear then that the greatest difficulty in diagnosis is associated with those smears diagnosed as consistent with adenocarcinoma.

L. M. HELLMAN.

Morris, John McL., and Meigs, Joe V.: Carcinoma of the Cervix. Statistical Evaluation of 1,938 Cases and Results of Treatment, Surg., Gynec. & Obst. **90**: 135, 1950.

In an extensive review of the 1,938 cases of carcinoma of the cervix in several hospitals in the vicinity of Boston, Mass., during the fifteen-year period from 1927 to 1942, the authors present statistical data of considerable interest. Most striking is the improvement in the five-year cure rate in all stages of this disease when the first five-year period of the study is compared with the last five-year period. Thus, the five-year cure rate in Stage I was 46 per cent from 1927 to 1931, and 60.3 per cent from 1938 to 1942. Similar improvement is shown for Stage II and Stage III and there is even a slight improvement in Stage IV. A discussion of radical surgery versus radiation is given. Because of the selection of patients for radical surgery no definite comparison with radiation series can be made but it is the opinion of the authors that while the results of radiation are known, those of radical surgery are yet to be explored.

L. M. HELLMAN.

Endocrinology

Smith, O. Watkins, and Smith, George Van S.: Use of Diethylstilbestrol to Prevent Fetal Loss From Complications of Late Pregnancy, New England J. Med. **241:** 562, 1949.

This communication from the Fearing Research Laboratory, Free Hospital for Women, the Boston Lying-in Hospital, and the Department of Gynecology, Harvard Medical School, deals with further progress in clinical evaluation concerning the action of diethylstilbestrol in human pregnancy.

The authors were particularly interested in its value for the prevention of complications of late pregnancy, essential hypertension, nephritis, or a past obstetric history or pre-eclampsia, eclampsia, premature delivery, or unexplained intrauterine death of the fetus.

They have emphasized the fact that whatever the primary etiologies of these complications may be, a premature deficiency of estrogen and progesterone sooner or later is involved and becomes an intermediate contributing factor, adequate vascularity being as essential for the normal production of the placental steroid hormones as adequate hormonal support for the increased vascular demands of the pregnant uterus. By supplying an extra stimulus for the secretion of estrogen and progesterone, they thereby are attempting to combat one of the contributory factors of the final syndrome.

Of 180 patients studied, 50 were given stilbestrol because of pre-existing hypertension, either essential or secondary to renal disease.

It was postulated that the uterine vascular deficiency associated with hypertension might at least be partially counteracted and obstetric complications thereby minimized by administration of stilbestrol.

In the past history of 105 pregnancies, there had been a 23 per cent fetal loss from spontaneous abortions and a further 30 per cent loss from late-pregnancy accidents. On stilbestrol therapy, 61 per cent of patients had no obstetric complications and 85 per cent gave birth to living children.

Sixty-six women had had pre-eclampsia, with 41 fetal deaths, a mortality rate of 43 per cent from this disease. The over-all fetal mortality from toxemia on stilbestrol therapy was 6.2 per cent.

Seventy-six women had had spontaneous premature deliveries in 83 per cent of their pregnancies prior to the one in which stilbestrol was administered. Forty-nine per cent again delivered prematurely despite therapy, however, the fetal loss was reduced from 77 per cent in the past to 20 per cent on stilbestrol therapy.

An interesting observation should be noted that the babies of stilbestrol-treated mothers are exceptionally heavy and long for their gestational ages and that, regardless of size, more of them survived than would have been expected from recent statistics on the mortality rates of premature infants.

In this statistical study, the authors were able to show a highly significant difference between treated and control cases in the matter of incidence and severity of toxemia and fetal loss from late-pregnancy complications when stilbestrol therapy was used.

JAMES P. MARR.

Perese, D. M., and Diddle, A. W.: Clinical Effect of Luteotrophin on Human Lactation, West. J. Surg. **57:** 576, 1949.

In an attempt to initiate and to stimulate lactation, the luteotrophin hormone in doses of 1,000 to 5,000 I.U. daily was given. In some patients the treatment was started prior to delivery, in others during the first few days post partum. Luteotrophin neither initiated lactation during the pregnancy nor earlier than usual during the postpartum period except in one doubtful instance. It is assumed that this hormone is ineffective for the stimulation of lactation.

One patient developed a marked urticaria, joint pains, and generalized edema as a result of sensitivity to the hormone.

WILLIAM BICKERS.

Jones, G. E. Seegar, Delfs, E., and Stran, H. M.: The Effect of Alpha-Tocopherol Administration on Pregnanediol Excretion, J. Clin. Endocrinol. 9: 743, 1949.

Because it has been clearly demonstrated by animal experimentation that a vitamin E deficiency is associated with sterility in the male and resorption of embryos in the female rat, vitamin E has been frequently used in the treatment of disorders of reproduction in the human being. There have been only six experiments reported on human beings in which simultaneous hormone excretion curves with vitamin E feedings have been carried out. Hence, it was thought worth while to establish any relationship between the administration of alpha-tocopherol and corpus-luteum function.

A series of well-controlled experiments were conducted in which the pregnanediol excretion was determined, using forty-eight hour specimens in every case. The blood-serum vitamin E levels were estimated as well.

The authors conclude that, while the amount of pregnanediol excreted varies greatly from cycle to cycle, there was no unusual variation when daily doses of 50 to 150 mg. of alpha-tocopherol were administered for one month. HERBERT J. SIMON.

Koets, Peter: The Excretion of 17-Ketosteroids in Idiopathic Hirsutism, J. Clin. Endocrinol. 9: 795, 1949.

A study of the urinary excretion of 17-ketosteroids in nine women with idiopathic hirsutism is presented. General physical examination in all nine patients failed to reveal any gross change in any organs or other cause for their condition. The ages of these patients varied from 21 to 30 years; none had children although several were married.

In normal women, the level of ketosteroid excretion during the menstrual cycle is, in general, constant. The excretion rate of 17-ketosteroids in two normal young women was determined at about ten-day intervals during the cycle and the known constancy was corroborated.

The nine patients complaining of idiopathic hirsutism showed: (1) the ketosteroid-excretion level to be well above normal range, (2) a cyclic variation in excretion associated with the menstrual cycle, and (3) the maximum excretion at the apparent time of ovulation.

The urinary ketosteroid-excretion pattern of normal female rats in relation to the estrus cycle was then studied. It was found that the excretion rate varied materially and that the maximum excretion occurred at mid-estrus which corresponds to the time of ovulation in woman. Thus, the excretion pattern of normal female rats simulates hirsute, rather than normal women. When the rats were ovariectomized, the cyclic variation of the excretion ceased and the level dropped materially.

From the foregoing, it was tentatively concluded that the increased 17-ketosteroid excretion in idiopathic hirsutism is the result of stimulation of the adrenal cortex by ovarian hormones. Further, the adrenal cortex in hirsute women is more sensitive to ovarian hormones than in normal women. HERBERT J. SIMON.

Endometriosis

Tyrone, Curtis, and Weed, John C.: Modern Trends in the Treatment of Pelvic Endometriosis, South. M. J. 43: 107, 1950.

Endometriosis is a clinical state which apparently is on the increase. This increase is thought to be related to the increased tension under which modern women are compelled to live. Pregnancy occurring early in the reproductive life appears to delay or indeed prevent the occurrence of the disease. The disease having become established, pregnancy is the best treatment. The surgical approach to pelvic endometriosis should bear this in mind and be directed toward increasing the probability of fertility. This point was emphasized in the discussion of the authors' paper and evidence presented to show that conserva-

tive surgery upon the ovaries is often followed by pregnancy. In the series of 583 proved cases which is here reported, conservative surgical measures were performed in only 68 patients, radical measures being applied to 515. This was thought by the discussers to be a high incidence of radical surgery. Medical treatment with stilbestrol was commented upon. WILLIAM BICKERS.

Counseller, Virgil S.: Surgical Procedures Involved in the Treatment of Endometriosis, Surg., Gynec. & Obst. **89**: 322, 1949.

This paper is based on surgical procedures on 852 patients occurring from 1940 through 1945. In this group, only 6.2 per cent were less than 30 years of age while 81.7 per cent were from 30 to 40 years. Over 56.7 per cent of these patients were submitted to radical operation. In the 13 per cent in whom conservative operation was done, 9 per cent had an additional presacral neurectomy for control of pain. Tubal operation was performed on 2 patients; oophorectomy in 27; salpingo-oophorectomy in 51; and local excision of tumor nodules in 27 instances. The author discusses the question of fertility in these cases and shows that in the group under discussion 737 were married with a sterility incidence of 29.2 per cent. The author feels that not more than 10 per cent who have been treated surgically will later become pregnant. L. M. HELLMAN.

Meigs, Joe Vincent: The Medical Treatment of Endometriosis and the Significance of Endometriosis, Surg., Gynec. & Obst. **89**: 317, 1949.

In an extremely thoughtful and contemplative article the author covers briefly the treatment of endometriosis with estrogens and testosterone. He feels that the hormonal approach may be palliative but not curative. With a brief glance to note the undesirability of x-ray castration in this young and sexually active group, he proceeds to a philosophical discussion of endometriosis and its social significance. Pointing out its sterilizing effect and its well-known proclivity for the private patient rather than the ward patient, he is disturbed by the fact that this disease is but one other added factor to the already diminishing birth rate of the upper middle class. As a cure he offers early marriage with parental financial support; early childbearing; and in late marriage no delay in reproduction. L. M. HELLMAN.

Gynecology

Speert, Harold: Ovarian Granulosa Cell Tumor and Acromegaly, J. Clin. Endocrinol. **9**: 630, 1949.

Amenorrhea is usually one of the first and most frequent symptoms of a pituitary tumor in women. This paper details a case in which there was a resumption of uterine bleeding as the result of a granulosa-cell tumor of the ovary.

The patient was a typical acromegalic of 42 years of age who gave a history of beginning menopausal symptoms four years earlier and amenorrhea for the past two years. However, for five or six months prior to admission to the hospital, the menopausal symptoms diminished in severity. The urinary estrogens were titrated and were elevated, thus demonstrating the functional activity of the tumor. At operation an endometrial polyp and a typical granulosa-cell tumor were found. The anticipated adenomatous hyperplasia of the endometrium was seen.

The endometrial polyp mentioned above was noted in at least three previous case reports of women suffering from acromegaly whose pelvic organs were examined. This, in spite of the fact that in relatively few cases of acromegaly have the pelvic organs been completely described. The more frequent occurrence of endometrial polyps than is normally encountered in women of this age group suggests an etiological relationship to the excessive secretion of the pituitary eosinophiles. The author states that this is the first recorded instance of a granulosa-cell tumor of the ovary in an acromegalic woman. HERBERT J. SIMON.

Gynecologic Operations

Edwards, Eugene A., and Beebe, Robert A.: Vaginal Hysterectomy, Surg., Gynec. & Obst. **89**: 191, 1949.

The authors report 570 vaginal hysterectomies performed at St. Luke's Hospital, Chicago, from Jan. 1, 1939, to Jan. 1, 1947. During the eight-year period covered, 27.5 per cent of the hysterectomies were performed by this route. However, during 1946, 48.2 per cent were done in this manner. This increase in the number of vaginal hysterectomies was due, in the authors' opinion, to increasing experience and a feeling that when feasible vaginal hysterectomy was much safer than operation by the abdominal route. They were able to show a lower incidence of postoperative complications, the chief of these being urinary tract infection. There was one operative death giving a mortality rate of 0.18 per cent. The authors feel that this operation gives better results in cases of prolapse than does the Manchester operation.

L. M. HELLMAN.

Labor, Management, Complications

Tucker, Beatrice E., Solomkin, Mark, and Abrams, Bernard: A Study of Face Presentation in the Normal Mature Fetus, Surg., Gynec. & Obst. **90**: 199, 1950.

In a study of sixteen and one-fourth years' experience at the Chicago Maternity Center, face presentation occurred 73 times in 39,687 deliveries. Of these 73 instances of face presentation, 64 occurred with normal mature infants; 6 occurred in primiparas; 58 in multiparas; there were 6 anencephalic monsters; and 3 were premature infants. The over-all incidence of face was 1 in 544 deliveries or if the series is corrected for the anencephalic monsters and the premature infants, the incidence is 1 in 620. This is a lower incidence of face presentation than found in any other series. It attests the normalcy of the patients delivered at the Chicago Maternity Center and is quite in keeping with the authors' contention that cephalopelvic disproportion did not occur in this series. In clinics, however, where contracted pelvis is present in a large proportion of cases, there can be no question that this entity plays an etiological role in the occurrence of face presentation.

The authors could find only two possible etiological factors: (1) multiparity, and (2) original occiput posterior position. Their infant mortality rate where uncorrected was 9.4 per cent. There were no maternal deaths. The authors are of the opinion that most patients will deliver spontaneously if allowed to do so and that this is the best method of handling this complication. There were 13 instances of persistent mentum posterior; in this group spontaneous rotation occurred in 53.8 per cent; in 6 the chin remained in the posterior position and operative delivery was necessary. Attempts at conversion were successful in only one instance in these 6 cases. Manual rotation if possible is advisable. Version and extraction were useful if done carefully, although one ruptured uterus occurred from this procedure.

L. M. HELLMAN.

Menstruation, Dysmenorrhea

Griffith, Mary I., and Little, J. Maxwell: Vasodilators in the Treatment of Functional Dysmenorrhea, South. M. J. **42**: 1082, 1949.

It is assumed that the pain of dysmenorrhea arises from compressed sensory nerve fibers in the blood-vessel wall of the uterus. Because of the original vasospasm it cannot be explained. A group of patients who have not responded to usual methods of treatment were given various vasodilating drugs on the theory that abolition of vasospasm would be followed by clinical relief.

Four patients were treated with Etamon but only one showed evidence of clinical relief of symptoms. Eighteen patients were treated with oral Priscoline with satisfactory clinical relief in 73 per cent. A combination of Priscoline and nicotinic acid gave complete or near complete relief in 97 per cent.

WILLIAM BICKERS.

Noyes, R. W., Hertig, A. T., and Rock, J.: Dating the Endometrial Biopsy, Fertility and Sterility **1**: 3, 1950.

The authors present a study of the histologic changes that take place in the endometrium during a complete normal menstrual cycle. The proliferative phase is divided into early, middle, and late stages, and the various criteria that identify each are depicted. During the secretory phase, changes in the endometrium are seen by which the authors believe they can recognize on which postovulatory day a specimen was taken. It was found that, in predicting the actual date of menstruation, maximum accuracy was attained by using the most advanced area in the biopsy for dating. The authors feel that in sterility studies the examination of secretory endometrium gives more information about the time of ovulation, the degree of progestational change, and the normality or abnormality of endometrium than any other single procedure.

N.B. This communication includes many excellent photomicrographs which greatly clarify and amplify the text; hence, no abstract can be adequate. HERBERT J. SIMON.

Placenta

Solomons, Edward: Calcification of the Placenta, Irish J. M. Sc., November, 1949.

In a previous paper in the *Irish Journal of Medical Sciences,* published in 1946, the author reported a case of marked placental calcification which occurred in two consecutive pregnancies in the same patient. In the first pregnancy, the fetus was born dead; in the second, a living child was obtained by cesarean section. In a brief paragraph the author now reports a third delivery of this same patient. This time labor was induced and a fetus, born after prolonged labor, was in poor condition and did not survive. Again the placenta showed marked calcification. L. M. HELLMAN.

Miscellaneous

Robbins, S. L., and Parker, F., Jr.: The Reliability of the Male North American Frog (Rana Pipiens) in the Diagnosis of Pregnancy, New England J. Med. **241**: 12, 1949.

This report is based on a study of three hundred consecutive urine tests submitted to the laboratory of the Mallory Institute of Pathology, Boston City Hospital. The animal used was the common leopard frog known as the *Rana pipiens.*

The authors admit that the Aschheim-Zondek test using immature rats is 99 per cent accurate, whereas their report reveals a 96 per cent accuracy.

The advantages of using the ordinary male frog are: (1) it is economical and the maintenance of a stock of available frogs in a small aquarium is easy; (2) in general, a positive reaction begins within thirty to forty-five minutes and persists for several hours. In general they represent "all-or-none" responses.

The analysis of the results indicates that most of the false-negative reactions, of which there were 13, were encountered in cases of normal pregnancy within the first month of amenorrhea, one at five weeks, and four between three and four months pregnant, which could be at least an embarrassing error.

However, to the authors the results obtained appear to justify the continued use and study of this diagnostic technique. Since the publication of this essay their technique has changed somewhat. Twenty c.c. of urine per frog are precipitated with 4 vol. of 95 per cent alcohol. The sediment obtained by vacuum filtration is dissolved in saline solution and injected. The results appear to be somewhat superior to those obtained with whole urine.
JAMES P. MARR.

Newborn

Allen, Fred H., Jr., Diamond, Louis K., and Watrous, Joseph B., Jr.: Erythroblastosis Fetalis. V. The Value of Blood From Female Donors for Exchange Transfusion, New England J. Med. **241:** 799, 1949.

A study of 205 babies with erythroblastosis fetalis indicates beyond reasonable statistical doubt that exchange transfusion of blood from female donors results in a lower mortality than that from male donors. Of 137 babies receiving blood from male donors only, 27 died, a mortality of 19.7 per cent. Of 42 babies receiving blood from female donors only, none died.

In addition to the series of 179 cases in which no attention was paid to the sex of the donor, 13 additional babies with erythroblastosis fetalis were deliberately treated with exchange transfusion using blood from female donors, with no deaths.

The beneficial component of such blood is not known, but isolated gamma fractions are being investigated. The authors state that whatever the beneficial component of blood from female donors as far as erythroblastosis is concerned, it must be shared by virtually all young adult females, since otherwise one would not expect so striking an effect from more-or-less random female blood donors.

This study is from the Blood Grouping Laboratory of Boston, Children's Medical Center, Boston, the Boston Lying-in Hospital, and the Departments of Pediatrics and Obstetrics, Harvard Medical School. JAMES P. MARR.

Swenson, Orvar, Rheinlander, Harold F., and Diamond, Israel: Hirschsprung's Disease: A New Concept of the Etiology. Operative Results in Thirty-Four Patients, New England J. Med. **241:** 551, 1949.

From The Children's Hospital, Children's Medical Center, and the Departments of Surgery and Pathology, Harvard Medical School, comes this report on the etiology and treatment of congenital megacolon, commonly known as Hirschsprung's disease. The latter published his classic description of this entity in 1888.

In the past, the emphasis on Hirschsprung's disease has been directed to the dilated and hypertrophied colon. It is the authors' contention that the primary lesion rests in the distal, nondilated segment. In eight patients with Hirschsprung's disease, they have recorded strong peristaltic waves in the dilated and hypertrophied colon. In none of the eight patients with Hirschsprung's disease did the peristalsis enter the narrow distal segment, which did exhibit inceased tonus.

This malfunctioning segment is identical with the narrow, irregular bowel visualized by roentgenograms. There appears to be a correlation between the absence of ganglion cells in areas of the rectosigmoid and the physiologic defect.

Removal of the narrow, irregular rectum and rectosigmoid by a special diagnostic and surgical technique in 34 patients has resulted in one postoperative death and what appear to be cures in 33 patients. JAMES P. MARR.

Pregnancy, Physiology

Waller, H.: The Early Yield of Human Milk, and Its Relation to the Security of Lactation, Lancet, p. 53, Jan. 14, 1950.

The volume of milk yield was determined in 400 women on the fifth and tenth postpartum days. These women were prepared during pregnancy by the use of a perforated plastic shield where necessary to improve prominence of the nipple, and by daily manual expression of colostrum, beginning during the thirty-second week of pregnancy. Lactating mothers were trained to express residual milk after breast feedings, and total output was estimated by adding this amount to that calculated by test weighing of the infant. It was shown that 78 per cent of these women produced enough milk for a 9 pound infant, by the tenth postpartum day.

The author feels that removal of residual milk does not artificially raise the total yield, but merely permits the breasts to reach full secretion. When breasts are laden with residual milk, secretion diminishes, and continues to fall below actual requirements. Failure to maintain an adequate yield is a more usual cause of artificial feeding than primary inability to lactate.

IRVING L. FRANK.

Knowlton, Abbie I., Mudge, Gilbert H., and Jailer, Jos. W.: Pregnancy in Addison's Disease, J. Clin. Endocrinol. **9**: 514, 1949.

While it is known that pregnancy may occur and progress to term in Addison's disease, it is, nevertheless, a serious complication of pregnancy. In the limited number of reports available, a deterioration of the health and often death of the mother have resulted.

Four patients with Addison's disease were studied during five pregnancies. Detailed case histories are given. Studies made on the urinary hormone excretion of these patients indicated that those substances derived from the placenta, i.e., gonadotropins, progesterone, estrones and estradiol, were excreted in normal or slightly decreased amounts. Thus, it may be concluded that a normal maternal adrenal cortex is not necessary for the placental production of adequate amounts of these hormones to maintain pregnancy.

The urine of one patient was assayed for corticoids, and none were found. Normally, there is a greatly increased amount, which was thought due to excretion by the fetal adrenals which are greatly enlarged at this time. It has been established, however, that the urine of newborn infants shows little or no corticoid activity. It would thus appear that the increased corticoids found normally in the urine of pregnant women is due to heightened function of the maternal adrenal cortex, rather than from the fetal adrenals. There is an increase in the secretion of 17-ketosteroids in pregnant women suffering from Addison's disease. It is suggested that the placenta contributes to this rise.

The management of pregnancy complicated by Addison's disease is discussed. The timely use of adrenal cortex hormones, sodium chloride by mouth and parenterally, plasma, and whole blood is urged.

HERBERT J. SIMON.

Arnold, G., Richer, A. G., and Lepore, J. J.: Suprarenal Hemorrhage in Pregnancy. Report of a Case With a Review of the Literature, New England J. Med. **240**: 1040, 1949.

The authors report a fatal case of intra-abdominal hemorrhage due to infarction of a right adrenal vein followed by rupture of the right adrenal gland. The patient with this unusual condition was admitted to the hospital because of severe persistent backache accompanied by pain over right costovertebral angle and to the right of the umbilicus. She was four months pregnant. The only other significant finding was an elevated blood pressure 158/70.

A normal appendix was removed at the first laparotomy, but a most extraordinary and misleading coincidence occurred. Blood was found issuing from a supposed endometriosis of the right ovary.

A subsequent laparotomy was performed because of rapidly deteriorating abdominal findings and the shocklike state of the patient, characterized by falling blood pressure and sudden severe anemia.

At autopsy, the right kidney was found encased by a large, reddish-brown, fluctuating mass, 20 cm. long and 10 cm. in thickness, composed of fluid and clotted blood. Section through this mass revealed a large, swollen, ruptured adrenal gland, 7 cm. long and 2 cm. thick.

The authors were able to collect 98 somewhat similar cases from the literature, which are well tabulated and analyzed. They also would remind us that we should include adrenal hemorrhage in the differential diagnosis of any uncertain abdominal situation.

JAMES P. MARR.

Downing, John Godwin, and Jillson, Otis F.: Herpes Gestationis. Fetal-Anomaly Syndrome Treated Successfully With Sulfapyridine, New England J. Med. 241: 906, 1949.

The case report from the Massachusetts Memorial Hospitals deals with a 41-year-old woman, 4½ months pregnant, who developed herpes gestationis during her second pregnancy. Local applications and antihistamines were of no avail. However, sulfapyridine in 0.5 Gm. dosage, three times daily, was most effective. At the end of three weeks the skin was entirely clear. Twice the sulfapyridine was discontinued and the dermatitis reappeared. On reinstitution of 0.5 Gm. three times a day, the eruption again completely cleared, and the patient eventually was delivered of a normal 8 pound boy.

In a statistical review of twenty cases of herpes gestationis appearing in thirteen women, it was found that the average time of onset was five and three-tenths months of pregnancy, and that eight of these women had histories of fetal anomalies.

JAMES P. MARR.

Hamilton, Hugh G., Pittam, Radford F., and Higgins, Robert S.: Active Therapy of Varicose Veins in Pregnancy, South. M. J. 42: 608, 1949.

Treatment in pregnancy of varicose veins which involve either the lower extremity or vulva is considered a safe procedure. In 591 cases in which active therapy of varicose veins in pregnancy was instituted, no patient aborted or had premature labor and there was no embolism. Treatment may be started at any period of gestation without fear of complicating the pregnancy.

In the discussion of this paper a more conservative attitude is taken. The policy of most obstetricians is that of conservative management until the pregnancy is physiologically terminated.

WILLIAM BICKERS.

Burch, Lucius E., and Burch, John C.: The Relation of Endometrial Hyperplasia to Menstrual Disorders, South. M. J. 43: 110, 1950.

Endometrial hyperplasia can be induced experimentally by the prolonged administration of gonadotropin from the anterior pituitary or by administration of the estrogens. This does not imply that endometrial hyperplasia is the result of overactivity on the part of either or both the pituitary and ovary. It does suggest, and there is adequate evidence to support the concept, that the hyperplasia results from prolonged stimulation of a noncyclic type. The periodic desquamation of the endometrium in the normal ovulatory cycle apparently prevents the development of hyperplasia. It follows, then, that endometrial hyperplasia is always an indication of ovarian failure. As the factor other than the hormone influences has not been well emphasized, namely, the vascular bed of the endometrium, the use of cyclical therapy in the form of estrogen and progesterone is often followed by readjustment of the pituitary ovarian endometrium system to the point where cyclic ovulation and cyclic bleeding occur. Prior to initiating cyclical treatment it is advisable to remove the superficial portion of the abnormal vascular bed by the surgical or medical curettage.

WILLIAM BICKERS.

Kaufman, Sherwin A.: A Consideration of the Midpelvis Among the Factors Which May Influence the Course and Outcome of Labor, West. J. Surg. 58: 14, 1950.

This report has to do with 100 obstetrical patients at or near term in whom there was an incidence of 30 per cent midpelvic contraction. The midpelvis was classified as "contracted" if the sum of the interspinous and posterior sagittal diameters was below 14 cm. The incidence of spontaneous delivery in the midpelvic contraction group was 70 per cent. The strength of uterine contractions appeared to be the determining factor. There was no correlation between midpelvic contraction and total duration of labor. X-ray study of the midpelvis may be valuable but it cannot be relied upon for prognosis as to the outcome of labor.

WILLIAM BICKERS.

Sterility, Contraception, Fertility

Brown, Willis E., and Bradbury, James T.: Management of Thyroid-Resistant Hypothyroid Women With Infertility, Fertility and Sterility **1**: 87, 1950.

The role of hypothyroidism in infertility and the interrelationship of the thyroid, the pituitary, and the ovary is generally discussed. The importance of diagnosing thyroid deficiency by clinical as well as laboratory studies is stressed. In addition, two conditions, hypothyroidism and hypometabolism are differentiated and clarified.

Two cases reports are then detailed. In both of these a low basal metabolism rate was unaffected by whole-gland thyroid therapy by mouth. However, when thyroxine by injection was administered, pregnancy ensued. The authors conclude that in certain patients, refractory to thyroid by mouth, parenteral thyroxine may be of value.

HERBERT J. SIMON.

Venereal Disease

Heyman, Albert, and McCain, John R.: Syphilis in Pregnancy. A Clinical Study of Factors Responsible for Congenital Syphilis, New England J. Med. **241**: 960, 1949.

This report emanates from the Departments of Medicine and Obstetrics, Grady Memorial Hospital and Emory University School of Medicine, and the Clinic for Genitoinfectious Diseases, Georgia Department of Public Health.

A clinical study of the factors responsible for the transmission of infantile congenital syphilis was made by a review of the records of 77 women who delivered syphilitic infants.

The diagnosis of congenital syphilis in the infants was based upon clinical findings, repeated quantitative serologic tests for syphilis, spinal-fluid studies, dark-field examinations, and roentgenographic examination of the long bones.

Almost all the patients in the group were infected before birth, since most of them showed overt manifestations of syphilis either at the time of delivery or very early in the neonatal period.

Twenty-one patients in this study were known to have had a negative serologic test in pregnancy but nevertheless delivered syphilitic children. Eighteen of these patients were either in the incubation period of the disease at the time or acquired an initial or recurrent infection later in pregnancy. From these findings the authors urge a repeated Kahn or Kolmer test as a routine procedure late in pregnancy, especially among a population with a high rate of syphilis.

The pregnant syphilitic woman has always been regarded as a potential source of infection for the fetus. For this reason, re-treatment of syphilis in pregnancy has been advised regardless of the amount of therapy the patient may have received previously. The adequacy of penicillin in protecting the fetus from syphilitic infection is well known.

The authors state that 16 of the 32 women who were treated in pregnancy had 11 or more injections of Mapharsen. To their surprise, several delivered syphilitic children.

Most workers now believe penicillin to be the drug of choice in prenatal syphilis. This form of therapy is not only more effective than arsenicals but also relatively nontoxic and can be given in a short period. Furthermore, it is valuable during the last trimester of pregnancy, a time when arsenical therapy is least useful.

In a few cases the attending physician did not establish the diagnosis of syphilis sufficiently early or did not institute immediate or vigorous antisyphilitic therapy. Several of these patients were attended by private physicians who neglected to take blood for serologic tests.

An occasional patient transmitted syphilis to her child even though she had had the disease for as long as eleven years previously.

An important measure in preventing congenital syphilis is greater education of pregnant women, who should be urged to seek prenatal care early in pregnancy.

In order to reduce the number of congenital syphilitic children, the authors recommend early attendance at prenatal clinics, repeated blood examinations late in pregnancy, and adequate penicillin therapy for antenatal syphilitics.

JAMES P. MARR.

Necrology

DR. JOHN CLARENCE WEBSTER, well-known gynecologist of Chicago before his retirement in 1919, died at his home in Shediac, New Brunswick, on March 16, 1950, at the age of 87 years. A graduate of the University of Edinburgh, Dr. Webster served as a lecturer there before coming to McGill University in Montreal, and then to Chicago, where he became professor of obstetrics and gynecology at Rush Medical College, as well as an attending physician at the Presbyterian Hospital.

After retiring, upon completion of twenty years in the latter capacity, to his place of birth in Shediac, he devoted himself to historical research, and the marking of famous historic sites in Canada. He had been a member of many medical societies, and was a Vice-President of the American Gynecological in 1920.

He was the co-author, with Dr. John M. Baldy of Philadelphia, of the uterine suspensory operation with which his name is linked.

WALTER WILLIAM CHIPMAN, noted obstetrician, gynecologist and teacher, died at his home in Montreal, April 4, 1950, at the age of 84 years. Born in Nova Scotia, he received his B.A. at Acadia College in 1890, the M.B.C.M. in Edinburgh, 1895, the degree of M.D. at McGill in 1908. Acadia University conferred upon him an LL.D. in 1913; Pittsburgh University in 1915; and the University of Wales in 1928. After serving as assistant to the lecturer in midwifery and diseases of women at the Edinburgh School of Medicine, Dr. Chipman came to Montreal where he founded the department of obstetrics and gynecology at McGill, and subsequently became obstetrician and gynecologist-in-chief at the Royal Victoria Montreal Maternity Hospital, retiring from active association with the institution in 1936, but remaining as Governor.

A Fellow of the British Gynecological Society, the Royal College of Surgeons (1933-1941), the American College of Surgeons (governor, and president, 1925), and the American Gynecological Society (president, 1921), Dr. Chipman made many outstanding contributions to the literature of his specialty, and was a notable orator. Dr. Chipman served as a member of the Advisory Editorial Board of the JOURNAL since its founding, and maintained a continuing interest in its progress.

"A great surgeon and a great gentleman" are the words which head an editorial in a Montreal newspaper about Dr. Chipman. To this may well be added other tributes that made his personality outstanding. He was a great humanitarian.

Items

Radioactive Isotopes

On Nov. 14, 1949, the Executive Board of the American Academy of Pediatrics approved the following recommendation of this Committee concerning the use of radioactive isotopes:

> "No Research Study with radioactive isotopes should be undertaken on pregnant women unless:
>
> (1) It cannot first be done on animals.
> (2) The study is approved by the Committee for Human Use of Radioactive Isotopes of the Atomic Energy Commission."

The recommendation was made because of the ready availability of certain radioactive isotopes at present.

The purpose of communicating this information to you is because this Committee believes the profession as a whole is unaware that it is now possible for an individual obtaining isotopes from a cyclotron to be the sole judge of how these substances are to be used.

HAROLD W. DARGEON, M.D., New York, N. Y.
Chairman, Committee for the Study of
Radioactive Effects in Childhood